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Evaluation Report ERC2011-02

Metconazole

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Overview

Registration Decision for Metconazole

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of Metconazole Fungicide Technical and Caramba Fungicide, containing the technical grade active ingredient metconazole, to control a variety of fungal diseases on barley, oats, rye, wheat, soybeans and sugar beets.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been found acceptable when all risk reduction measures are followed, the registrant must submit additional scientific information as a condition of registration.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of metconazole and Caramba Fungicide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* (PCPA) is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children), as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's Web site at healthcanada.gc.ca/pmra.

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[1] "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

[2] "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

What Is Metconazole?

Metconazole is a triazole fungicide (DMI; demethylation-inhibiting fungicide) that inhibits sterol biosynthesis. The end-use product, Caramba Fungicide, is a chemical fungicide that contains 90 g/L metconazole formulated as an emusulfiable concentrate for use on barley, oats, rye, wheat, soybeans and sugar beets to control or to suppress certain foliar fungal diseases.

Health Considerations

Can Approved Uses of Metconazole Affect Human Health?

Metconazole is unlikely to affect your health when used according to label directions.

Potential exposure to metconazole may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when metconazole products are used according to label directions.

The technical grade active ingredient metconazole was moderately toxic to rats and highly toxic to mice when given as a single oral dose. It was of low dermal and inhalation toxicity. It was slightly irritating to the eyes of rabbits and a potential skin sensitizer to guinea pigs. The signal words, "DANGER – POISON", "EYE IRRITANT" and "POTENTIAL SKIN SENSITIZER" have been included on the label in light of these findings. The end-use product, Caramba Fungicide, was found to be of low oral, dermal and inhalation toxicity in rats. It was an eye irritant in rabbits, was not dermally irritating to rabbits and not a dermal sensitizer in guinea pigs. The signal words, "WARNING – EYE IRRITANT" were required.

Although metconazole was not genotoxic, it did cause cancer in mice, but not in rats. A cancer risk assessment was conducted based on the skin tumours found in the mouse.

The first signs of toxicity in animals given daily doses of metconazole over longer periods of time were decreased body weights, effects in blood (regenerative anaemia) and microscopic changes to the liver, spleen and adrenal glands. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

When metconazole was administered to pregnant animals, an increase in cranio-facial malformations was observed. These effects were observed at doses that were not toxic to the mother, indicating that the foetus is more sensitive to metconazole than the adult animal. Due to the serious nature of these endpoints, extra protective factors were applied during the risk assessment to further reduce the allowable level of human exposure to metconazole.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Refined aggregate dietary intake estimates (food plus water) revealed that the general population and children, the subpopulation that would ingest the most metconazole relative to body weight, are expected to be exposed to less than 33.9% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from metconazole is not of concern for all population sub-groups. The lifetime cancer risk from the use of metconazole on all supported food uses is considered acceptable.

A single dose of metconazole is not likely to cause acute health effects. Aggregate (food and water) dietary intake for females 13-49 years old was 50.1% of the acute reference dose, which is not a health concern.

The *Food and Drugs Act* (FDA) prohibits the sale of adulterated food, namely, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for FDA purposes through the evaluation of scientific data under the PCPA. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

The majority of the residue trials were conducted in the United States using metconazole on barley, oats, rye, wheat, soybeans and sugar beets. The MRLs for this active ingredient can be found in the Science Evaluation section of this Evaluation Document.

Occupational Risks From Handling Caramba Fungicide

Occupational risks are not of concern when Caramba Fungicide is used according to the label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply Caramba Fungicide as well as field workers re-entering freshly treated fields can come in direct contact with metconazole residues on the skin. Mixers, loaders and applicators may also be exposed by breathing sprays and mists. Therefore, the label specifies that anyone mixing, loading or applying Caramba Fungicide or performing clean-up or repair activities must wear coveralls over long-sleeved shirt, long pants, chemical-resistant gloves, socks and footwear, except for aerial applicators who must wear long-sleeved shirts, long pants, socks and footwear. Closed cabs are required for all groundboom applications. Closed mixing/loading systems are required when handling more than 164 L of Caramba Fungicide per day. The label also requires that workers do not enter treated fields for 4 to 9 days after application depending on the crop treated. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the risk to workers handling Caramba Fungicide is not of concern.

For bystanders, exposure is expected to be much less than for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Metconazole Is Introduced Into the Environment?

Metconazole is toxic to non-target terrestrial plants and aquatic organisms. It is persistent in soil and aquatic sediment; however, it is not persistent in water. Metconazole is a potential leacher and may reach groundwater. Label instructions, including spray buffer zones, are required.

Metconazole enters the environment when used as a fungicide on agricultural crops including barley, oats, rye, wheat, soybeans and sugar beets. Metconazole is moderately persistent to persistent in the terrestrial environment. It is relatively stable to hydrolysis and phototransformation, undergoing minor biotransformation in both soil and water. Despite its high soil absorption, metconazole has the potential to leach into groundwater due to its solubility in water, persistence in sediment, low volatility and stability (however, residues in groundwater were not above the level of concern for human health). Based on its low volatility (low vapour pressure and Henry's law constant), metconazole residues are not expected in the air, nor is long-range aerial transport expected. Specific instructions to prevent carryover, groundwater contamination and runoff into aquatic habitats are provided on the end-use product label.

Metconazole presents a negligible risk to terrestrial invertebrates including earthworms and honeybees, terrestrial vertebrates including small wild mammals and birds, freshwater invertebrates including daphnids, marine invertebrates including mysid shrimps and molluscs, juvenile stages of freshwater fish, freshwater algae, marine fish and marine algae. However, it may adversely affect non-target terrestrial plants, amphibians, early life stages of freshwater fish and freshwater aquatic vascular plants. Therefore, toxicity statements for non-target terrestrial plants and aquatic organisms are specified on the product label. Spray buffer zones are also required to protect terrestrial, freshwater and estuarine/marine habitats adjacent to areas treated with metconazole fungicide.

Value Considerations

What Is the Value of Caramba Fungicide?

Caramba Fungicide suppresses Fusarium head blight (*Fusarium graminearum*) on wheat, barley, rye and oats, and controls Septoria leaf blotch (*Septoria tritici*), leaf rust (*Puccinia recondita*) and tan spot (*Pyrenophora tritici-repentis*) on wheat, Asian soybean rust (*Phakospora pachyrhizi*) on soybeans and Cercospora leaf spot (*Cercospora beticola*) on sugarbeets.

Caramba Fungicide is an additional product for Canadian growers, in particular the cereal, soybean and sugar beet industries. The active ingredient of Caramba Fungicide, metconazole, belongs to the triazole group (Group 3) and has been classified as having a moderate risk for resistance development. Moreover, Caramba Fungicide can be an important tool when used in an IPM program in conjunction with other elements such as resistant varieties, cultural controls and predictive models.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Caramba Fungicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

A Plant Back Interval of 35 days is required for all crops not listed on the label.

As there is a concern with users coming into direct contact with Caramba Fungicide on the skin, anyone mixing, loading and applying Caramba Fungicide must wear coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks and footwear, except for aerial applicators who must wear long-sleeved shirts, long pants, socks and footwear. Closed cabs are required for all groundboom applications. Closed mixing/loading systems are required when handling more than 164 L of Caramba Fungicide per day. The label also requires that workers do not enter treated fields for 4 to 9 days after application depending on the crop treated. In addition, standard label statements to protect against drift during application were added to the label.

Environment

A hazard statement to inform the user that this product is toxic to non-target terrestrial plants and aquatic organisms is required. Guidance to reduce runoff from treated areas into aquatic areas as well as a precautionary statement to avoid groundwater contamination, especially in areas with sandy soils, is also required. In addition, spray buffer zones up to 40 m in size are required for aerial application and up to 15 m in size for ground application in order to protect sensitive aquatic habitats.

What Additional Scientific Information Is Being Requested?

Although the risks and value have been found acceptable when all risk-reduction measures are followed, the registrant must submit additional scientific information as a condition of registration. More details are presented in the Science Evaluation of this Evaluation Report or in the section 12 Notice associated with these conditional registrations. The registrant must submit the following information within the time frames indicated.

Human Health

- The registrant is required to submit a modified plant analytical method for D0508 that reflects the recommendation of the ILV laboratory and is reviewed by the registrant's quality assurance unit. Additionally, the registrant must provide a confirmatory method either by modifying the method to provide information on a second MS/MS ion transition or an alternate chromatographic system.
- The registrant is required to submit a validated animal enforcement method.
- Metconazole must be tested through a valid and appropriate multiresidue method.
- Rotational crop studies are considered conditionally acceptable pending the submission of acceptable freezer storage stability data for M11 in wheat forage stored frozen for up to 21 months, as well as for *cis*- and *trans*-metconazole in wheat grain and straw stored frozen for up to 18 months, in wheat forage and radish tops stored frozen for up to 21 months, and in lettuce stored frozen for up to 19 months.
- Confirmatory crop field trials for barley, oats, rye and wheat conducted at the Canadian rate of 90 g a.i./ha in Canadian representative growing regions are required. For barley, 5 field trials conducted in NAFTA Region 14 are required. For oats, 4 field trials conducted in NAFTA Region 14 are required. For rye, 1 field trial conducted in NAFTA Region 7, and 2 field trials conducted in NAFTA Region 14 are required. For wheat, 2 field trials conducted in NAFTA Region 7, 1 field trial conducted in NAFTA Region 7A, and 3 field trials conducted in NAFTA Region 14 are required.

Environment

- Non-target freshwater invertebrate study: Acute and chronic ecotoxicity study exposing chironomids to metconazole.
- Fish life cycle toxicity test: Chronic ecotoxicity study exposing all life stages of fish to metconazole.

Value

To support aerial application, at least three confirmatory trials are required comparing efficacy of Caramba Fungicide when applied with high water volume (a minimum of 100 L of water per ha) versus low water volume (50 L of water per ha) on one of the crop/pest combinations listed on the Caramba Fungicide label (namely, barley/fusarium head blight, wheat/fusarium head blight, sugar beets/Cercospora leaf spot, etc.). Data should be submitted within 2 years after registration.

Other Information

As these conditional registrations relate to a decision on which the public must be consulted[3], the PMRA will publish a consultation document when there is a proposed decision on applications to convert the conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

The test data cited in this Evaluation Report (namely, the test data relevant in supporting the registration decision) will be made available for public inspection when the decision is made to convert the conditional registrations to full registrations or to renew the conditional registrations (following public consultation). If more information is required, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.infoserv@hc-sc.gc.ca).

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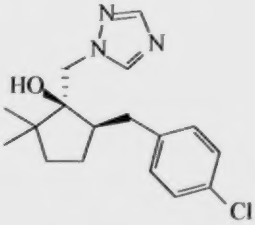
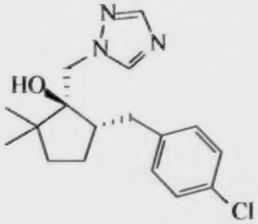
[3] As per subsection 28(1) of the *Pest Control Products Act*.

Science Evaluation

Metconazole

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Metconazole	
Function	Fungicide	
Chemical name		
1. International Union of Pure and Applied Chemistry (IUPAC)	(1*RS*,5*RS*;1*RS*,5*SR*)-5-(4-chlorobenzyl)-2,2-dimethyl-1-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentanol	
2. Chemical Abstracts Service (CAS)	5-[(4-chlorophenyl)methyl]-2,2-dimethyl-1-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentanol	
CAS number	125116-23-6	
Molecular formula	C17H22ClN3O	
Molecular weight	319.83	
Structural formula	 cis-metconazole (1RS,5RS)	 trans-metconazole (1RS,5SR)
Purity of the active ingredient	97.0% nominal	

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Product—Metconazole Technical

Property	Result
Colour and physical state	White solid
Odour	Odourless
Melting range	100.0 – 108.4°C
Boiling point or range	N/A
Specific gravity	1.14
Vapour pressure at 20°C	Analyte — Vapour pressure (Pa) AI — < 1.23 ×10-5 *cis*-isomer — < 1.04 ×10-5 *trans*-isomer — < 1.96 ×10-6
Ultraviolet (UV)-visible spectrum	λmax = 221.4 nm
Solubility in water at 20°C	Analyte — Solubility (µg/mL) AI — 30.4 *cis*-isomer — 17.1 *trans*-isomer — 13.6
Solubility in organic solvents at 20°C (mg/mL)	Solvent — AI — *cis* — *trans* acetone — 363 — 251 — 117 methanol — 403 — 291 — 117 2-propanol — 132 — 86.6 — 46.7 ethyl acetate — 260 — 173 — 90 methylene chloride — 481 — 343 — 141 toluene — 103 — 66.2 — 38 hexane — 1.4 — 0.929 — .483
n-Octanol-water partition coefficient (K_{ow})	— K_{ow} — log K_{ow} AI — 7090 ± 989 — 3.85 *cis* — 7150 ± 803 — 3.85 *trans* — 6800 ± 1700 — 3.8
Dissociation constant (pK_a)	pKa1 = 11.38 ± 0.03 pKa2 = 1.06 ± 0.03
Stability (temperature, metal)	The product was found to be stable in the presence of metals in their natural state (aluminum and iron) and their ionic form (aluminum acetate and iron acetate) at normal and elevated temperature (25 ± 2°C and 54 ± 2°C, respectively).

End-Use Product—Caramba Fungicide

Property	Result
Colour	Not provided
Odour	Not provided
Physical state	Liquid
Formulation type	Emulsifiable concentrate
Guarantee	90 g/L (limits: 85.4 – 94.6 g/L)
Container material and description	High-density polyethylene (HDPE) jugs or totes, 0.100–1000 L, 8.1 L, 16.2 L
Specific gravity	1.046
pH of 1% dispersion in water	6.0 at 20°C
Oxidizing or reducing action	The product does not react with iron, a reducing agent. It reacts very weakly with oxidizing agents and with water.
Storage stability	The product was shown to be stable for 208 weeks when stored at 20°C in HDPE packs.
Corrosion characteristics	No corrosive effects from the product have been observed in the package tested for 208 weeks.
Explodability	The product has no explosive properties.

1.3 Directions for Use

On cereals and sugar beets, Caramba Fungicide may be applied prior to disease development or at the onset of disease symptoms. On soybeans, Caramba Fungicide can be applied from vegetative through the full seed stage. When applied according to the use directions on barley, oats, rye and wheat, Caramba Fungicide can provide control of leaf rust (*Puccinia recondita*), tan spot (*Pyrenophora tritici-repentis*) and septoria leaf spot (*Septoria tritici* or *Stagonospora nodorum*). Caramba Fungicide also suppresses fusarium head blight (FHB) on wheat and barley. When applied as indicated on the label, Caramba Fungicide can control Asian soybean rust (*Phakopsora pachyrhizi*) on soybeans, and cercospora leaf spot (*Cercospora beticola*) on sugar beets.

1.4 Mode of Action

The active ingredient of Caramba Fungicide, metconazole, inhibits the Cytochrome P450-depedent 14-demethylase (DMI) reaction in the sterol biosynthesis pathway, as is the case for many other fungicidal azoles. This blockage of the sterol biosynthesis leads to a reduction in the normal sterol pathway end products and an accumulation of other abnormal sterols. Blockage of the synthesis of ergosterol, an important structural component of many fungal cell membranes, controls fungal growth and development by interfering with synthesis of new membrane needed for cell growth.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Metconazole Technical have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

Metconazole was not fully tested through multi-residue analytical methodologies as described by the USFDA Pesticide Analytical Manual, Vol. I. Therefore, the behaviour of metconazole through these protocols is unknown. German multiresidue method DFG S19 is not recognized as a multiresidue method in Canada and is therefore considered as supplemental information.

2.3.1 Methods for Residue Analysis in Environmental Media

High-performance liquid chromatography method with tandem mass spectrometry (HPLC-MS/MS) and two gas chromatographic methods with nitrogen phosphorus (GLC-NPD) detection were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in soil, sediment and water. Methods for residue analysis are summarized in Appendix I, Table 1.

2.3.2 Methods for Residue Analysis in Plant Matrices

Although, several analytical methods were used for data gathering purposes in plant matrices, no method was proposed for enforcement. Method D0508 uses liquid chromatography with tandem mass spectrometry to determine residues of *cis*- and *trans*-metconazole, as well as, metabolites M11, M21, M30, 1,2,4-triazole (1,2,4-T), triazolylalanine (TA) and triazolylacetic acid (TAA) in plant matrices. The limit of quantitation was reported as 0.01 ppm each for metconazole (sum of 0.005 ppm for each isomer), M11, M21 and M30. The limit of quantitation was reported as 0.05 ppm each for 1,2,4-T, TA and TAA. The method was adequate with regards to specificity, accuracy and precision at the limits of quantitation. Acceptable recoveries (70-120%) of all analytes were obtained in plant matrices. Method D0508 could be used as the enforcement method for plants, provided the registrant: 1) modifies the method such that information for a second MS/MS ion transition can confirm the identity of the analytes or provides an alternate chromatographic column and or mobile phase combination; 2) incorporates the recommendations of the ILV laboratory in an official enforcement method document and provides the required information to demonstrate the extraction efficiency of the method.

2.3.3 Methods for Residue Analysis in Animal Matrices

Although, several analytical methods were used for data gathering purposes in animal matrices, no method was proposed for enforcement. Data gathering method RM-41M-1 uses gas chromatography with a nitrogen phosphorous detection system to determine residues of *cis*- and *trans*-metconazole in dairy matrices. Data gathering method RM-41M-2 uses liquid chromatography with tandem mass spectrometry to determine residues of *cis*- and *trans*-metconazole in animal tissues. Data gathering method RM-41M-3 uses liquid chromatography with tandem mass spectrometry to determine residues of M1 and M12 in animal tissues. The limit of quantitation was reported as 0.02 ppm for each isomer of metconazole as well as M1 and M12 in all bovine matrices (milk, muscle, fat, kidney and liver) except for cream which had a reported limit of quantitation of 0.04 ppm. Acceptable recoveries (70-120%) of all analytes were obtained in animal matrices. The methods were adequate with regards to specificity, accuracy and precision at the limits of quantitation, however, none of the methods were adequately radiovalidated or subjected to ILV.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for metconazole was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to this chemical pest control product.

Metconazole technical is comprised of a mixture of the *cis* and *trans* isomers at a minimum w/w ratio of 80:20. The majority of the studies were performed using this mixture; however, the bile cannulation study and the triazole-14C metabolism studies were performed on the *cis* isomer only. Comparison of the cyclopentyl-14C mixture and triazole-14C *cis* isomer metabolism studies indicated that there was not a large difference in metabolism.

Acute studies indicated that metconazole was of high oral toxicity to mice, moderate oral toxicity to rats, low dermal toxicity to rats, low dermal toxicity to rabbits and low inhalation toxicity to rats. Metconazole was moderately irritating to the eyes of rabbits. It was not irritating to the skin of rabbits and was a potential skin sensitizer in guinea pigs.

The end-use product, Caramba Fungicide, was of low oral, dermal and inhalation toxicity in rats. It was moderately irritating to the eyes of rabbits. It was not irritating to the skin of rabbits and not a skin sensitizer in guinea pigs. The *cis* isomer was not a dermal sensitizer in guinea pigs. A plant metabolite, AC381390, designated M11 in residue definitions, was of low oral toxicity in rats.

Metconazole was extensively absorbed in both male and female rats; however, systemic exposure was greater in females than males since females reabsorb metconazole after biliary excretion and further metabolise the compound. Elimination was rapid, extensive and predominantly through the faeces via biliary excretion, though females excreted more metconazole in the urine than males. The principal organs of distribution were the adrenal glands, liver and gastrointestinal (GI) tract with reservoirs in the blood, kidney, skin and fat. There was some potential for bioaccumulation. The proposed metabolic pathway for the *cis* isomer was a monohydroxylation followed by a carboxylation. The major metabolites were M1, a monohydroxy metabolite, and M12, a carboxy-metabolite, though the characterization of the metabolites was poor and only performed on the *cis* isomer.

In all species tested, there were durational effects with metconazole administration in the target organs of the liver, adrenals and reproductive organs, as well as signs of irritation and regenerative anaemia. In the liver, adaptive changes were evidenced as increased weight, enzymes and vacuolation, as well as hypertrophy and Kupffer-cell pigmentation. Necrotic changes consisted of focal, strangulated and single cell necrosis. Proliferative changes consisted of multifocal or oval cell hyperplasia or biliary proliferation. Changes to the adrenals consisted of weight increases, cortical vacuolation and cortical hypertrophic foci. In the mouse 91-week study only, medullary hyperplasia of the adrenals was also seen. In general, throughout the database, changes to the haematopoietic system indicated regenerative anaemia, with some combination of decreases in erythrocyte and haemoglobin parameters, changes to the platelet counts, increases in differential white blood cell counts, spleen weights and gross and histopathological changes to the spleen, such as atrophy or prominent trabuculae and stroma in the spleen, congestion and histiocytic foci. Signs of irritation consisted of leukocytic foci in various organs, congestion/haemorrhage and red foci in the urinary bladder and stomach, nephritic damage, gastritis in the stomach, avillous plaques in the GI tract and congestion/haemorrhages in the caecum. Although there were some sex differences in the toxicity profile, one was not more susceptible to toxicity than the other.

In the rat, toxicity in the dermal study was limited to increased clotting times and adaptive changes to the liver at the limit dose.

In the short-term rat studies, there was dose-related progression from adaptive liver changes to hepatotoxicity and necrosis. The liver was the primary target organ, though there were also effects on body weights and food consumption, effects on the adrenal glands including increased weight and cortical vacuolation, reproductive organs including decreased weights and reduced spermatozoa and evidence of regenerative anaemia at doses above the LOAELs. In the 28-day study, there were effects on the kidneys including decreased weights in males and signs of nephrotoxicity. At the highest dose tested in the 90-day study, there was additionally white matter vacuolation of the spinal cord in males and a satellite recovery group showed incomplete recovery of the affected organs.

The rat chronic toxicity and oncogenicity studies were conducted concurrently in the same lab. The dose selection was identical with the exception that the chronic toxicity study included an additional low dose group. When the liver and adrenal findings were compared and combined from the two studies, there was vacuolation of the adrenals in both sexes and necrotic changes to the liver in males at the 100 ppm dose group at the end of the 104 week period. There was evidence of a durational effect with adaptive changes to the liver at interim sacrifice at lower doses than the 28 and 90-day studies. Signs of haematopoietic change occurred at the mid-dose and at lower doses than in the shorter term studies. At the mid-high dose, there were changes to the kidneys, signs of irritation in the small intestines and hyperplasia in the testes in males. At the top dose, there were also changes to the spinal cord in males, urinary system, thyroid and reproductive organs. There were no treatment-related increases in tumours in the rat.

In the mouse 90-day oral study, decreased cholesterol and bilirubin, increased creatinine, liver weights and hepatocellular hypertrophy and vacuolation, occurred concurrently with decreased body weights in males and spleen effects in males and females at the mid-dose. At the high dose, in addition to the changes in the liver, there was evidence of regenerative anaemia and further adaptive changes in the liver.

In the mouse 91-week study, at the lowest dose tested, there was evidence of regenerative anaemia in both sexes, increased adrenal weights, increased liver weights and focal necrosis in males and decreased body weight gain in females. At the mid-dose, body weight gains were decreased in both sexes, there were adaptive and necrotic changes in the liver of both sexes, evidence of haematopoietic change in both sexes including effects on the bone marrow in males, effects on the adrenal glands, hyperplasia in the ovaries and some pigmentation changes in the kidneys. At the high dose, body weights were decreased in males and females and food consumption was decreased; there were extensive changes to the haematopoietic system, extensive necrotic and proliferative changes to the liver, changes to the lymph nodes, enlarged thyroids, extensive changes to the reproductive systems and hyperplasia in the adrenals. In addition to nephropathy, at the highest dose tested there was evidence of irritation in the urinary and gastro-intestinal systems and leukocyte foci in a wide variety of organs, including the brain. This may indicate a possible metabolite causing irritation leading to long-term systemic damage.

In the mouse 91-week study, there were neoplasms in the liver and skin. In the liver, adenomas and carcinomas were increased above concurrent controls at the highest dose tested and skin sarcomas were increased above concurrent controls at all doses tested. The skin sarcomas occurred at a frequency of 0, 3.9, 5.9 and 9.8% of the animals in doses 0, 30, 300 and 1000 ppm respectively. This exceeded the historical control values of 1.5 – 2.0% in all dose groups.

In a battery of genotoxicity tests, the overall outcome was negative. The gene mutation and *in vivo* unscheduled DNA synthesis tests were negative. The *in vitro* mammalian chromosomal aberration test was positive at low concentrations with metabolic activation and negative without. The *in vivo* mammalian cytogenetics test was negative with some reservations regarding the study conduct.

A 2-week hepatic drug-metabolizing study was performed to further investigate the liver tumours in the high-dose mice. It was found that, while there were effects on enzymes and reactive oxygen species production, proliferation occurred only in the high-dose animals. While the liver adenomas and carcinomas were treatment-related, progression from hepatotoxicity to liver tumours only occurred at the highest dose tested which exceeded the maximum tolerated dose.

Therefore, these liver tumours were not considered relevant for human risk assessment. However, although the overall genotoxicity profile indicated no risk of a genotoxic mechanism of action for metconazole, no mode of action data was submitted for the skin sarcomas and a threshold could not be established. In the absence of a mode of action, by default, a quantitative risk assessment was performed.

In the dog 28-day study, clotting times and thyroid weights were increased at the mid-dose in females. At the high dose, body weights were decreased, there were haematopoietic changes, adaptive liver changes and increased heart and testes weights in the males. In the 90-day oral toxicity study, there were decreased body weights, increased platelet counts and thyroid weights and evidence of irritation in the urinary bladder at doses three times lower than the LOAEL in the 28-day study. In addition, at the high dose, there were body weight changes, eye effects, evidence of regenerative anaemia, adaptive liver changes, irritation in the nephritic and urinary systems and increased adrenal weights. In the 12-month study, the same changes were noted at mid-high and high doses. However, ovarian weights were increased in high-dose animals as opposed to the testicular weight increases seen in the shorter study.

There were two repeat-dose neurotoxicity studies performed in rats. In the 2-week study, the pattern of toxicity matched that seen in the short-term oral studies. Changes in functional behaviour only occurred at very high doses and consisted of increased elevated, high-stepping or abnormal gait, increased response to tail pinch and decreased high beam and increased low beam breaks. The latter finding may be a result of the decreased body weights and reduced palatability of the diet that led to increased foraging behaviour. In the 4-week study, doses were lower and the only evidence of toxicity was decreased body weights and food consumption. There was evidence of nerve degeneration in the 90-day oral toxicity study and in the long-term studies at interim sacrifice; however, these occurred only in the presence of other systemic toxicity effects.

The results of the reproductive toxicity study in the rat indicated that there was systemic toxicity in the dams at the mid-dose with increases in the thyroid weights and reproductive effects. At the high dose, both males and females showed adaptive changes in the liver and one female exhibited hepatocellular necrosis. Females also exhibited weight and hypertrophic changes to the adrenal glands and increases in splenic weights and congestion and there was an increase in pelvic dilatation in male kidneys. Female reproductive changes consisted of increased ovary weights at the mid- and high-doses and an increase in mortality during parturition and increases in follicular and lutein ovarian cysts and gestation indices at the high dose. Males showed an increase in prostate weights at the mid- and high-doses. In the rest of the database, there are indications of effects on the male reproductive system, such as reductions in the amount of spermatozoa in the urine and changes in gonad and accessory organ weights, along with adrenal changes. In light of these changes, although sperm counts and motility were unaffected in this study, effects of metconazole on male reproductive toxicity cannot be discounted. In the offspring, at the high dose, there were decreases in the number of pups born live, increases in the number of pup deaths and decreased live birth, survivorship and viability indices. Post-natal body weight gain was decreased and there was an incident of kinked tail which may be related to the spinal cord malformations seen in the rat developmental toxicity study. Increased spleen weights, white spots on the liver and dilated renal pelvises indicated that metconazole affects the same target organs in the offspring as the adults.

There was a supplementary oral study performed in rats to investigate changes in the maternal hormones and the increase in mortality during parturition noted in the multigeneration reproductive toxicity study. Liver enzymes (CYP 2B1) were increased at the lowest dose tested with microsomal protein levels and cytochrome P-450 increased at the mid-dose. At the high dose, body weight, body weight gains and food consumption were decreased and there was an increase in hair loss. Liver weights were increased along with CYP 2B1 levels. In the ovaries, relative weights were increased with a decrease in corpora lutea, an increase in cell proliferation within the corpora lutea, a decrease in 17β-estradiol and E/P ratios and an increase in progesterone. This was correlated with a decrease in implantations per dam and live foetuses and an increase in resorptions and foetal deaths.

In the rat developmental toxicity study, maternal toxicity was marked by decreased body weights at the mid-dose and increased placental weights and foetal toxicity was marked by an increase in malformations of the spinal column consisting of rudimentary or threadlike tails or agenesis of the tail with imperforate anuses in the presence of maternal toxicity. At the high doses, there was an incident of maternal mortality as well as decreased body weights, gravid uterine weights and food consumption. Dark content was found in the ileum and caecum; there was an increase in swollen spleens and an increase in early and late resorptions and post-implantation loss. In addition, there was a decrease in foetal body weights, a single incident of malrotated hindlimbs (linked to vertebral column malformations) and an increase in variations.

Two sets of developmental toxicity studies were performed on the *cis:trans* isomer mixture with rabbits. In the first study, maternal toxicity consisted of dose-related increases in total and late resorptions at the LOAEL for maternal toxicity. At higher doses, there were decreases in food consumption leading to anorexia at the highest dose tested. At maternally non-toxic levels, there was an increase in craniofacial abnormalities and an increase in subcapsular liver cysts in the foetuses. At maternally toxic doses, there was a skewing of the sex ratios in favour of males and an increase in corneal/lenticular opacity in the foetuses. At the higher doses, there were increases in the foetuses of cervical ribs, umbilical hernias and reduced gastro-intestinal tracts. At the highest dose, there was a decrease in foetal weights. In a later developmental toxicity study, foetal toxicity only occurred in the presence of maternal toxicity. At the maternal and foetal LOAEL, which was equivalent to the maternal LOAEL in the first study, there was increased post-implantation loss. At higher doses, maternal creatinine phosphokinase enzymes were increased leading to greater liver changes at the highest dose tested along with evidence of regenerative anaemia. In the foetuses, there were increases in dilation of the lateral brain ventricles at the LOAEL. At higher doses, gravid uterine weights were decreased and there was a foetus with circumcorneal haemorrhage and spina bifida. At the highest dose, there was a skewing towards males in the sex ratio, an increase in cervical ribs and a single incidence of shortened tail. Single incidences of circumcorneal haemorrhage, spina bifida and shortened tail were considered treatment-related due to the presence of similar malformations in other studies. In light of craniofacial malformations in other conazoles (e.g., tebuconazole, prothioconazole, diniconazole and epoxiconazole) the results of the first study were considered to be most relevant to the risk assessment.

Of the six rabbit developmental studies submitted, three were performed on the *cis:trans* mixture, two were performed on the *cis* isomer in isolation and one study was performed with the *cis*, (-) *cis* and *trans* isomers on six females/dose/isomer. Results of the studies on the mixture and separate isomers support the applicants' claim that the *cis* isomer is the most developmentally toxic of the isomers. In a study of the three isomers, the *cis* and (-)*cis* isomers caused an increase in anorexia and abnormal faeces in dams at the low and mid-dose, respectively, and cold ears at the mid-dose. At the high dose in the *cis* isomer study, there were decreases in body weight and body weight gain, increased abortions, decreased litters, litter size and number of foetuses and an increase in dead foetuses and post-implantation loss. Developmental changes consisted of an increase in cranial and hind-limb malformations at the mid-dose. With the (-)*cis* isomer, high dose changes consisted of a decrease in maternal body weight gain and food consumption, a decrease in live foetuses and an increase in post-implantation losses. In the foetuses, cranial and hindlimb defects were noted at the mid-dose and high dose. With the *trans* isomer, there were anorexia and abnormal faeces noted at the mid-dose and body weights gains were decreased in the dams at the high dose, but there were no effects in the foetuses. Further studies were performed on the *cis* isomer, where the first signs of toxicity in the dams were body weight losses and an increase in late resorptions, followed by cold extremities, an increase in post-implantation losses and a decrease in live foetuses at higher doses. However, increases in limb malformations were noted in the absence of maternal toxicity and cranial and spinal column malformations were noted in the presence of maternal toxicity, along with variations in the liver.

3.1.1 PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to take into account completeness of the data with respect to the exposure of and toxicity to infants and children and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database, the data are adequate for determining pre- and post-natal toxicity. There was a 2-generation reproductive toxicity study along with a supplementary study investigating hormonal changes in the rat during gestation. There were preliminary and definitive rat developmental toxicity studies. The rabbit developmental toxicity studies consisted of one preliminary study and two definitive studies on the *cis:trans* isomer mixture and two studies on the *cis* isomer and a study of the *cis*, (-)*cis* and *trans* isomers.

With respect to identified concerns relevant to the assessment of risk to infants and children, in the rat studies, there were decreases in survival and birth indices at the offspring LOAEL, and there were increases in terminal spinal column malformations at the rat developmental LOAEL. These endpoints occurred at maternally toxic doses in the rat and at doses greater than the doses producing malformations in rabbits. Sensitivity of the young was identified in a rabbit developmental toxicity study, in which serious effects were noted in the offspring (i.e., craniofacial malformations) at a maternally non-toxic dose.

Although similar craniofacial malformations did not occur in the second rabbit developmental toxicity study, craniofacial malformations have been observed in other conazole pesticides and the increase in malformations in the first rabbit developmental study was considered treatment-related. This information was taken into account in determining the appropriate factors in the risk assessment.

Results of the acute and repeat-dose tests conducted on laboratory animals with metconazole technical and its associated end-use products, along with the toxicology endpoints for use in the human health risk assessment, are summarized in Appendix I, Tables 2, 3, and 4.

3.2 Determination of Acute Reference Dose (ARfD)

ARfD determination for females aged 13–49

The NOAEL of 2 mg/kg bw established in the first rabbit developmental toxicity study is considered appropriate for the determination of the ARfD for females 13 – 49. At the LOAEL of 4 mg/kg bw/day, there was an increase in craniofacial malformations in the developing foetus in the absence of maternal toxicity. As outlined in section 3.1.1, the PCPA factor was retained at 10-fold along with the standard uncertainty factors of 10-fold for inter-species extrapolation and 10-fold for intra-species variability. The composite assessment factor (CAF) is 1000.

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{2\text{ mg/kg bw}}{1000} = 0.002\text{ mg/kg bw}$$

ARfD determination for the general population (excluding females aged 13 – 49)

Based on the toxicological profile for metconazole, no ARfD for the general population is required.

3.3 Determination of Acceptable Daily Intake (ADI)

ADI determination for females aged 13 – 49

The NOAEL of 2 mg/kg bw/day established in the first rabbit developmental toxicity study is considered appropriate for the establishment of an ADI. At the LOAEL of 4 mg/kg bw/day, there were increased craniofacial malformations in the absence of maternal toxicity. The applied factors included the standard 100-fold uncertainty factor to account for the inter-species extrapolation and intra-species variability, and the aforementioned PCPA factor of 10-fold. The CAF is 1000. The ADI proposed for females aged 13 – 49 is:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{2\ \text{mg/kg bw/day}}{1000} = 0.002\ \text{mg/kg bw/day}$$

ADI determination for the general population (excluding females aged 13 – 49)

In determining the ADI, the results of the rat chronic and oncogenicity studies were considered together. The NOAEL of 0.44 mg/kg bw/day was established based on incidences of adrenal cortex vacuolation and clear cell foci and necrotic inflammatory foci in the liver.

The ADI is 0.0044 mg/kg bw/day, based on the standard uncertainty factor of 100 to account for the inter-species extrapolation and intra-species variability. The PCPA factor is reduced to 1-fold because the database is considered appropriate with regards to pre- and post-natal toxicity and the endpoint of concern with respect to pre- and post-natal toxicity has been addressed in a population specific risk assessment (i.e. females aged 13 – 49). The composite assessment factor is 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{0.44\ \text{mg/kg bw/day}}{100} = 0.0044\ \text{mg/kg bw/day}$$

Cancer Risk Assessment

In the absence of mode of action data on the skin sarcomas in male mice to support a threshold approach to the cancer risk assessment, a linear low dose extrapolation approach (q_1*) was used for metconazole. Unit risks for metconazole, denoted by q_1* (representing the upper 95% confidence limit on the slope of the dose-response curve in the low-dose region), were calculated on the basis of the bioassay data from the 91-week carcinogenicity study in mice. An adjusted q_1* value of 1.02×10^{-2} (mg/kg bw/day)$^{-1}$ was derived in male mice based on the increased incidence of skin sarcomas.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Occupational exposure to metconazole is characterized as short- to intermediate-term and is predominately by the dermal and inhalation routes for chemical handlers and by the dermal route for workers re-entering treated areas.

The NOAEL of 2 mg/kg bw/day from the first rabbit developmental toxicity study is considered the most appropriate endpoint for occupational risk assessment. The NOAEL is based on the observation of craniofacial malformations in foetuses in the next higher dose level of 4 mg/kg bw/day (LOAEL). In addition, the value of 2 mg/kg bw/day is similar to the next lowest short-term NOAELs of 2.73 mg/kg bw/day observed in male rats in the 28-day oral toxicity study and 2.5 mg/kg bw/day observed in female beagle dogs in the 28-day oral toxicity study. The worker population could include females of child bearing age (13 – 49). For this reason, the residual uncertainty with respect to the possibility of effects in developing offspring is relevant, and an additional 10-fold factor is considered appropriate. The target Margin of Exposure (MOE) is 1000, accounting for standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as the additional 10-fold factor. The selection of this study and MOE is considered to be protective of all populations including nursing infants and the unborn children of exposed female workers.

3.4.1.1 Dermal Absorption

An *in vivo* dermal absorption study was provided, in which male Crl:Wi (Han) rats were administered nominal doses of 2.25 and 600 µg a.i./cm^2 of metconazole (85:15 *cis:trans* isomer ratio) in the form of an emulsifiable concentrate. One hundred µL of the dosing solution was applied to approximately 10 cm^2 of the skin on the rat's back. Three groups of four rats in each dose group were monitored up to 120 hours. The application site of all the rats was washed after six hours of exposure. Recoveries ranged from 104 – 111%. Calculated dermal absorption was the sum of the residues found in the urine, cage wash, faeces, carcass, blood, plasma, skin on the application site, and the surrounding skin. The dermal absorption values were corrected for the high amount of residue found in protective cover and glass ring washings. Mean dermal absorption estimates for rats in the low dose group were 26%, 17% and 21% when sacrificed at six hours, 24 hours and 120 hours, respectively. Mean dermal absorption estimates for rats in the high dose group were 22%, 6.3% and 15% when sacrificed at six hours, 24 hours and 120 hours, respectively. Given the variability in actual deposition under field conditions, it is considered appropriate to derive an estimate of dermal absorption based on the low dose groups, as percent dermal absorption was greatest at the low dose level. In addition, since a longer post-exposure period provides more information about the fate of absorbable and absorbed dose over time, the dermal absorption was derived based on groups sacrificed at 120 hours. The dermal absorption estimate of 21% from the low dose group at 120 hours sacrifice was considered most appropriate to adopt for risk assessment purposes.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/loader/applicator (M/L/A) Exposure and Risk Assessment

Individuals have potential for exposure to Caramba Fungicide during mixing, loading and application. As chemical-specific data for assessing human exposures were not submitted, dermal and inhalation exposures for workers were estimated using the Pesticide Handlers Exposure Database (PHED) Version 1.1. PHED is a compilation of generic mixer/loader and applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates.

Exposure to workers mixing, loading and applying Caramba Fungicide is expected to be short- to intermediate-term in duration and to occur primarily by the dermal and inhalation routes. In Appendix I, Table 5, exposure estimates were derived for mixer/loaders/applicators applying Caramba Fungicide to cereals, soybeans and sugar beets by ground or aerial application while

- Wearing cotton coveralls over single layer plus gloves when mixing/loading.
- Wearing cotton coveralls over single layer when applying by ground boom.
- Wearing a single layer when applying by air.
- Applying in a closed cab when using groundboom.
- Mixing using open pour or closed mixing/loading systems.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day and the dermal absorption value. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 70 kg adult body weight.

Non-Cancer Risk Assessment

Exposure estimates were compared to the toxicological endpoint (NOAEL = 2 mg/kg bw/day) to obtain the margin of exposure (MOE); the target MOE is 1000 (Appendix 1, Table 6). The risk estimates for all M/L/A exposure scenarios are summarized in Table 3.4.1.

Table 3.4.1 Non-cancer risk estimates for mixer/loader and applicator scenarios

Crops	Margin of exposure for specified scenario*					
	M/L/A Farmer (open pour)	M/L/A Custom (open pour)	M/L/A Custom (closed M/L)	Aerial M/L (open pour)	Aerial M/L (closed M/L)	Aerial A
Cereals (to suppress fusarium head blight)	1535	456	1387	459	1827	1853
Wheat (to control leaf diseases)	2193	652	1981	655	2611	2647
Soybeans	2193	652	1981	655	2611	2647
Sugar beets	1228	365	1109	367	1462	1482

M/L/A = Mixer/loaders and applicators, M/L = Mixer/loaders, A = Applicator

All margins of exposure (MOEs) were calculated for workers wearing coveralls over single layer and chemical-resistant gloves except for aerial applicators (single layer). For M/L/A farmer and custom, MOEs were calculated for workers using closed cab tractors.

* Based on NOAEL = 2 mg/kg bw/day, target MOE = 1000, from rabbit developmental study

MOEs are acceptable for farmers but not acceptable for custom applicators when open pouring because custom applicators generally handle more product per day. When workers handle more than 164 L of Caramba Fungicide (14.78 kg of metconazole per day) when open pouring in coveralls over single layer and gloves, MOEs do not reach the target MOE of 1000 (Appendix I, Table 7). As such, workers must use closed mixing/loading systems when handling more than 164 L of Caramba Fungicide per day.

Cancer Risk Assessment

To calculate the potential lifetime exposure of agricultural workers handling Caramba Fungicide, mixer/loader/applicator exposures are amortized over an individual's lifetime. This is expressed as the lifetime average daily dose (LADD), which takes into account multiple exposure scenarios and the frequency of exposure scenarios throughout the individual's lifetime.

The LADD was calculated assuming a worst-case scenario; i.e. farmers can apply the maximum number of applications per year for a crop, and custom applicators, as well as aerial mixer/loaders and applicators, can apply on a daily basis throughout the growing season, with the exception of weekends. Based on the production characteristics for the crops and application timings, it was estimated that custom applicators could apply Caramba Fungicide between three days per year and 146 days per year. Farmers, custom applicators, and aerial mixer/loaders and applicators could potentially have a working tenure of 40 years and life expectancy is assumed to be 75 years. Cancer risk was estimated by multiplying the LADD by the q1* value of 1.02 x 10-2 (mg/kg bw/day)-1.

The M/L/A cancer risk assessment was conducted for chemical handlers (Appendix 1, Table 8). Calculated cancer risk estimates for all M/L/A scenarios are below 1 x 10-5 (ranging from 7.62 x 10-9 to 1.46 x 10-6) and are therefore considered acceptable (Table 3.4.2).

Table 3.4.2 Cancer risk for mixer/loader and applicator scenarios

Crops	**Lifetime cancer risk for specified scenario***			
	M/L/A Farmer	**M/L/A Custom**	**Aerial M/L**	**Aerial A**
Cereals (to suppress fusarium head blight)	1.09×10^{-8}	4.30×10^{-8}	3.89×10^{-8}	3.84×10^{-8}
Winter wheat (to control leaf diseases)	7.62×10^{-9}	1.46×10^{-6}	1.33×10^{-6}	1.31×10^{-6}
Spring wheat (to control leaf diseases)	7.62×10^{-9}	8.33×10^{-7}	7.53×10^{-7}	7.43×10^{-7}
Soybeans	1.52×10^{-8}	7.72×10^{-7}	6.99×10^{-7}	6.89×10^{-7}
Sugar beets	2.72×10^{-8}	1.36×10^{-6}	1.23×10^{-6}	1.21×10^{-6}

All lifetime cancer risk estimates were calculated for workers wearing coveralls over single layer and chemical-resistant gloves except for aerial applicators (single layer). Risk estimates were calculated for custom applicators and aerial mixer/loaders using closed mixing/loading systems. For M/L/A farmer and custom, risk estimates were calculated for workers using closed cab tractors.

*Cancer risk estimates less than 1x 10^{-5} are considered acceptable.

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers re-entering areas treated with Caramba Fungicide. Postapplication activities are limited to scouting and occasional irrigation, since all crops are mechanically harvested.

Dermal exposure to workers entering treated areas is estimated by coupling dislodgeable foliar residue (DFR) values with activity-specific transfer coefficients. Chemical-specific dislodgeable foliar residue data were not submitted. As such, default values of 20% of application rates on the day of application and a default daily dissipation rate of 10% were used to estimate dislodgeable foliar residues for the exposure assessment. Exposure was adjusted using a dermal absorption of 21% and normalized by using 70 kg adult body weight. Workers are assumed to be performing postapplication activities in the treated crops for four hours per day.

Non-Cancer Risk Assessment

Exposure estimates were compared to the toxicological endpoint (NOAEL = 2 mg/kg bw/day) to obtain the MOE; the target MOE is 1000. Postapplication exposure was calculated for the day of the last application (Appendix I, Table 9). Exposure estimates on the day of last application were below the target MOE of 1000 for all uses (summarized in Table 3.4.3). Therefore, restricted entry intervals (REIs) are required for all crops.

Table 3.4.3 Non-cancer postapplication risk estimates for re-entry workers scouting and irrigating

Crops	Margin of exposure* (on the day of application)	Required restricted entry interval (REI) to meet target MOE
Cereals (to suppress fusarium head blight)	617	5 days
Soybeans	654	4 days
Sugar beets	402	9 days

* Based on NOAEL = 2 mg/kg bw/day, target MOE = 1000, from rabbit developmental study

Cancer Risk Assessment

To calculate the potential lifetime exposure of agricultural workers to metconazole residues as a consequence of postapplication activities (i.e., scouting and irrigation), exposures are amortized over an individual's lifetime. This is expressed as the LADD and takes into account the frequency of exposure throughout the individual's lifetime.

The LADD was calculated based on the assumption that Caramba Fungicide may be applied to crops at the earliest possible time with scouting occurring until harvest. Based on the production characteristics for the crops and potential application timing, the number of days workers scout is between 100 days and 168 days per year.

To calculate postapplication cancer risk, the time-weighted average (TWA) DFR was used, which is the average of the DFR values from the first application (when scouting begins) to the harvest (when scouting ends). Workers are assumed to have a working tenure of 40 years and life expectancy of 75 years. The cancer risk was estimated by multiplying the LADD by the q1* value of 1.02 x 10-2 (mg/kg bw/day)-1.

The postapplication cancer risk assessment is presented in Appendix I, Table 10. Calculated cancer risk estimates for all scenarios are below 1 x 10-5 (ranging from 1.55 x 10-7 to 8.63 x 10-7), and therefore are considered acceptable (Table 3.4.4).

Table 3.4.4 Postapplication cancer risk estimates for re-entry workers scouting and irrigating

Crop(s)	Calculated cancer risk*
Cereals (to suppress fusarium head blight)	3.44×10^{-7}
Winter wheat (to control leaf diseases)	1.55×10^{-7}
Spring wheat (to control leaf diseases)	2.40×10^{-7}
Soybeans	4.83×10^{-7}
Sugar beets	8.63×10^{-7}

*Cancer risk estimates less than 1×10^{-5} are considered acceptable.

3.4.3 Residential Exposure and Risk Assessment

3.4.3.1 Handler Exposure and Risk

Caramba Fungicide is not a domestic class product; therefore, a residential handler assessment was not required.

3.4.3.2 Postapplication Exposure and Risk

Caramba Fungicide is not to be used in residential settings; therefore, a residential postapplication assessment was not required.

3.4.4 Bystander Exposure and Risk Assessment

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application is limited to agricultural crops only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for enforcement in plant products and animal commodities is *cis*- and *trans*-metconazole. The residue definition for risk assessment in plant products, except barley, oats, rye and wheat is *cis*- and *trans*-metconazole, and is *cis*- and *trans*-metconazole plus M11 in barley, oats, rye and wheat. The residue definition for risk assessment in animals is *cis*- and *trans*-metconazole plus M1, M1 aglycone, M31, M31 aglycone and M12.

The data gathering analytical methodologies adequately quantify residues of *cis*- and *trans*-metconazole, M11, M21, M30 and triazole metabolite residues in banana, barley, oats, rye, soybeans, sugar beets and wheat. The methods also adequately quantify residues of *cis*- and *trans*-metconazole, M1 and M12 in livestock matrices.

Residues of *cis*- and *trans*-metconazole were stable when frozen for 26 months in radish roots, soybean seed and wheat hay; 12 months in carrot, lettuce, rapeseed, rapeseed oil, rye forage, wheat grain, wheat straw; six months in banana. Residues of M11, M21 and M30 were stable when frozen for 26 months in radish tops, sugar beet roots, soybean seed and wheat grain, hay and straw. Residues of 1,2,4-T were stable when frozen for 26 months in radish tops and soybean seed and 12 months in wheat grain and radish root.

Residue data from trials conducted in NAFTA representative growing regions at exaggerated rates using end-use products containing metconazole on barley, oats, rye, wheat, soybeans and sugar beets are sufficient to support the conditional registration of Caramba Fungicide and the establishment of MRLs. Residue data from banana trials conducted in Mexico, Ecuador, Costa Rica and Honduras are sufficient to support the establishment of MRLs to cover metconazole residues in/on imported bananas.

The metabolism of metconazole in rotational crops is similar to that observed in primary crops. Metconazole was identified at 30- and 120-day plantback intervals (PBIs) in all rotational crop matrices except triazole-labelled wheat grain where TA and TAA were the major metabolites. Based on the field crop rotation studies, a plantback restriction of 35 days for crops not listed on the label will be required.

As a result of processing raw agricultural commodities residues of *cis*- and *trans*-metconazole concentrated in wheat AGF (64.3-fold), husks (121.4-fold), bran (1.9-fold) and middlings (2.0-fold) as well as in soybean hulls (1.7-fold) and in sugar beet pulp (1.9-fold), dried pulp (14-fold), thick juice (1.3-fold), molasses (1.9-fold) and raw sugar (2.2-fold). No separate MRLs are required for edible processed fractions, as their residues will be covered by MRLs established on the corresponding raw agricultural commodities.

The potential for secondary transfer of metconazole residues into fat, meat, meat byproducts, milk and eggs exists because there are feed items associated with the proposed use on barley, oats, rye, wheat, soybean and sugar beets. Based on the results of the cattle feeding study and hen metabolism study, residues of *cis*- and *trans*-metconazole are expected to be below the limit of quantitation in animal matrices.

3.5.2 Dietary Risk Assessment

Acute and chronic (cancer and non-cancer) dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.0), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.5.2.1 Chronic Dietary Exposure Results and Characterization

A refined chronic dietary assessment was performed using median residue trial data, anticipated residues in animal commodities (fat, meat, meat byproducts, milk and eggs), experimental processing factors and percent crop treated data. Refined estimates of the chronic dietary exposure to metconazole from all supported food uses ranged from 2.7 - 15.6% of the ADI. Aggregate exposure to metconazole from food and water ranged from 9.2 - 33.9% of the ADI and is considered acceptable.

3.5.2.2 Acute Dietary Exposure Results and Characterization

A refined acute dietary assessment (deterministic; 95th percentile) was conducted for females 13 - 49 years old using maximum residue trial data, anticipated residues in animal commodities (fat, meat, meat byproducts), experimental processing factors and percent crop treated data. The aggregate acute dietary exposure estimate for females 13 - 49 years old from all supported food uses and water was 50.1% of the ARfD and is considered acceptable.

3.5.2.3 Lifetime Cancer Risk Results and Characterization

For the general population, the estimated lifetime cancer risk from exposure to metconazole was refined as described for the chronic assessments. The estimated lifetime cancer risk from exposure to metconazole was 1.89 x 10-6 for food and 5.30 x 10-6 for food and water. The refined estimates are considered acceptable and protective of human health for the following reasons:

- The residue inputs used were derived from cereal crop field trials performed at exaggerated rates (2-3 fold) that are reflective of the United States GAP. As more than 98% of wheat, rye, oats and barley originate domestically, the dietary exposure to metconazole from imported cereal grains are expected to be minimal.

- Anticipated residues in animal matrices are overestimated since they are based on cereal crop field trials that were performed at exaggerated rates (2-3 fold). Additionally, percent crop treated (CT) data were not incorporated into maximum reasonably balanced diet calculations. Finally, cereal feed items, treated at exaggerated rates, are not expected to be imported as animal feed.

- Metconazole residues in banana were less than LOQ at exaggerated rates, therefore anticipated residues in banana are expected to be well below LOQ when banana plants are treated at the GAP of the exporting countries. Additionally, 100% CT was assumed for all imported bananas.

- In general metconazole residues declined with increasing PHIs. Therefore, crops harvested after the minimum PHI are expected to have lower levels of metconazole residues by the time they reach commercial channels.

3.5.3 Maximum Residue Limits

Table 3.5.1 Proposed Maximum Residue Limits

Commodity	Recommended MRL* (ppm)
Banana	0.1
Barley	2.5
Oat	1
Rye	0.25
Wheat	0.15
Soybean	0.05
Sugar beets roots	0.15
Eggs	0.04
Milk	0.04
Fat, Meat and Meat, byproducts	0.04

* MRL established to cover residues of *cis-* and *trans-*metconazole.

The nature of the residues in animal and plant matrices, the analytical methodology, the field trial data, and the acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 11 and 12. For additional information on MRLs in terms of the international situation and trade implications refer to Appendix II.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Metconazole enters the Canadian environment when used as a fungicide on agricultural crops including cereals (wheat, barely, oats, and rye), soybeans and sugar beets. Metconazole is moderately persistent to persistent in both terrestrial soil and in aquatic sediment systems. It has slight to low persistence in water. Metconazole has one major transformation product in soil (M30) and one major transformation product in an aquatic/sand sediment system (M13).

Metconazole is persistent in soil. Laboratory studies indicate that slow aerobic soil biotransformation is the only important route of metconazole transformation with half lives ranging from 618 to 661 days for the soil study submitted. One major transformation product, M30 was found at a maximum of 13.5%, and several minor transformation products were found at maxima that did not exceed 10% of total residues.

Metconazole is persistent in water/sediment systems. Laboratory studies indicate that aerobic aquatic biotransformation is also slow, with whole system half-lives of 151 to 900 days. The only major transformation product found in the total system was M13 at a maximum of 10.9% of total residues. Metconazole is less persistent in water than in soil or sediment. Dissipation half-lives in water were much faster (0.81 – 15.9 days), with movement from the water phase to the sediment phase, and then persistence in the sediment phase (aerobic biotransformation half-lives of 206 – 534 days in sediment). Under anaerobic conditions in a water/soil sediment system, the anaerobic biotransformation rate in water was DT50 4.57 days and DT90 36.6 days. The anaerobic biotransformation rate for the soil and the total system was estimated to be greater than the study duration of 120 days. Under anaerobic conditions in a water/clay sediment system, the phase transfer DT50 was less than one hour in water, and the DT50 was greater than 365 days in clay sediment and total system.

Metconazole is stable to hydrolysis at environmentally relevant pH, and it does not readily undergo the process of phototransformation (half-lives in laboratory soil and water systems were 300 days and 43 days, respectively). Thus, hydrolysis and phototransformation are not important dissipation routes for metconazole.

Metconazole has two p*K*a values (11.38 and 1.06), both of which indicate that this compound will be present in its non-dissociated form at environmentally relevant pH; and due to its neutral charge, pH levels should not affect the mobility of metconazole in soil.

Metconazole displays slight to low mobility in soil based on adsorptive characteristics derived from laboratory studies, and according to the mobility classification scheme of McCall *et al.* (1981). However, despite the low soil mobility, there are a number of properties which favour leaching (solubility in water, persistence in sediment, hydrolytic and photolytic stability, and low volatility). Thus, the leaching indicators (Cohen *et al.*, 1984; and Gustafson, 1989) show that metconazole has the potential to leach. Despite this leaching potential, the level of concern for metconazole residues in drinking water was not exceeded (see sections 3.5.2.2 and 3.5.2.3).

Data from a northern United States field dissipation study (conducted in an ecoregion relevant to Canada), showed metconazole to be moderately persistent in the top 0 - 7.5 cm soil layer. It was not detected below the 15 cm level of the soil profile and transformation products were not detected. The DT50 and DT90 were of 119 days and 396 days, respectively. There was 12% carryover into the next growing season and 3.9% carryover of metconazole residues after 641 days.

The low vapour pressure (1.23 x10-5 Pa at 20 °C) and Henry's law constant (2.08 x 10-9 atm-m3- mol^{-1}) indicate that metconazole is non-volatile under field conditions and from water and moist soil surfaces. Therefore, metconazole residues are not expected to volatilize in the atmosphere, nor is long-range aerial transport expected as a result of volatilization.

Although the *n*-octanol-water partition coefficient indicates that there may be a potential for bioconcentration in organisms (log *K*ow 3.85), results from laboratory studies in fish show a maximum biological concentration factor (BCF) of 218, followed by 99% depuration within 14 days, indicating that bioaccumulation is not a concern for metconazole.

Data on the environmental fate and behaviour of metconazole are summarized in Appendix I, Table 13 (terrestrial) and Table 14 (aquatic).

4.2 Effects on Non-Target Species

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are calculated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments are adjusted according to Appendix I, Table 15, to account for potential differences in species sensitivity as well as varying protection goals (that is, protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Effects on Terrestrial Organisms

Metconazole enters the terrestrial environment when used as a fungicide on agricultural crops including cereals (wheat, barely, oats, and rye), soybeans and sugar beets. The risk to non-target terrestrial organisms was based upon the use pattern for the end-use product, Caramba Fungicide, and the evaluation of ecotoxicity data for the following organisms:

- One earthworm species and one bee species representing invertebrates (acute studies);
- Two bird and two mammal species representing vertebrates (acute, short-term dietary, reproduction, and developmental toxicity studies);
- Ten crop species representing non-target terrestrial vascular plants (seedling emergence and vegetative vigour studies).

Terrestrial organisms such as earthworms, honeybees, birds, small mammals and terrestrial plants may be exposed to Caramba Fungicide in the environment through direct application, contact with treated material, or (in the case of birds and mammals) from ingestion of contaminated food. The screening level risk quotients for Caramba Fungicide were based on the seasonal maximum application rate (two single applications of 112.5 g a.i./ha, for a total seasonal maximum of 225 g a.i./ha).

The ecological risk assessment of metconazole to terrestrial organisms was conducted by first evaluating the ecotoxicity data for invertebrates, vertebrates and plants (Appendix I, Table 16). After determining the most sensitive ecotoxicity endpoints, these values were then incorporated into the deterministic risk quotient for the screening level risk assessment (Appendix I, Tables 18 and 19). In those cases where the screening level assessments resulted in the level of concern being exceeded, a refined assessment was conducted to further characterize the risk to terrestrial organisms (Appendix I, Table 21).

The proposed use of metconazole is not expected to pose a risk to terrestrial invertebrates including earthworms and honeybees. The results of the earthworm ecotoxicity study showed no significant mortality or decrease in body weight at the highest test concentration (1000 mg a.i./kg dw). Risk quotients calculated at the screening level (incorporating direct exposure to the proposed maximum application rate of 225 g a.i./ha) did not exceed the level of concern for earthworms. For honeybees, the ecotoxicity study LD50 values were > 100 µg a.i./bee and 86 µg a.i./bee for acute contact and acute oral exposure, respectively. Thus, metconazole was classified as relatively non-toxic. At the proposed application rate, the screening level risk quotient values were less than the level of concern for honeybees.

The proposed use of metconazole is not expected to pose a risk to birds when exposed by acute or short-term ingestion. All screening level risk quotient values for acute, short-term dietary and reproductive effects were less than the level of concern.

The acute oral toxicity to bobwhite quail was studied using two kinds of metconazole, an isomeric ratio: metconazole 85:15 (*cis:trans*), and metconazole 95% (*cis*). The acute oral LD50 values for the isomeric mix and *cis* isomer were 798 and 875 mg a.i./kg bw, respectively while the NOEL values based on body weight change were less than 450 and 450 mg a.i./kg bw, respectively.

The acute dietary toxicity to birds was studied by exposing bobwhite quail and mallard duck to an isomeric mix of metconazole. For bobwhite quail, the acute dietary LC50 was 1057 mg a.i./kg diet and the NOEC based on body weight change was less than 165 mg a.i./kg diet. For the mallard duck, the LC50 was greater than 5230 mg a.i./kg diet and the NOEC based on weight loss was 1370 mg a.i./kg diet.

The reproductive toxicity to birds was studied by exposing bobwhite quail and mallard duck to an isomeric mix of metconazole. No reproductive effects were noted for the mallard duck at the highest dose tested, 240 mg a.i./kg diet. In the reproductive study with the bobwhite quail, effects on embryo success, hatching success, chick survival and chick weight were observed at the highest dose tested, 120 mg a.i./kg diet and the NOEC for reproductive endpoints was therefore established at 60 mg a.i./kg diet. The risk quotient values did not exceed the level of concern for bird reproduction.

Based on acute oral toxicity studies using laboratory rats and mice, and multi-generational studies on laboratory rats, the proposed use of metconazole is not expected to pose a risk to small wild mammals.

For rats, the NOAEL was 660 mg/kg bw, and for mice, the NOAEL was 566 mg/kg bw (both values are for combined sexes). The end-use product, Caramba Fungicide, was also tested on rats under acute oral conditions. The NOAEL was found to be 3526 mg/kg bw for male rats and 2102 mg/kg bw for female rats. According to the study results, the end-use product, Caramba Fungicide, is less toxic than the technical grade active ingredient, metconazole. Risk quotient values for both the end-use product and the active ingredient did not exceed the level of concern.

The reproductive toxicity of metconazole was examined for rats using a multi-generational study. Ecologically relevant effects including increased mortality during parturition, a decreased gestational index, and decreased number of pups delivered were seen at 750 ppm (43.2/63.2 mg/kg bw/day). Thus, the reproductive NOEL was 150 ppm (9.05/12.67 mg/kg bw/day). The screening level risk quotient values for reproductive effects did not exceed the level of concern.

When metconazole is applied at 109 g a.i./ha (which is just slightly below the one-time application rate), there are slight toxic effects on plants. In the seedling emergence test, phytotoxic effects included reductions in plant height for the radish (11%), cabbage (11%) and wheat (5%). For the vegetative vigour test, crop plants affected by Caramba Fungicide treatment included reductions in cabbage dry weight and plant height (12%), and radish dry weight (14%). Out of the 10 crop species tested, representing non-target terrestrial plants, none showed 25% reduction in growth measurements. Thus, an EC25 could not be obtained from both the vegetative vigour and seedling emergence studies.

Screening level risk quotients were above the level of concern (partially due to the fact that the tests were conducted at the one-time application rate and not the seasonal maximum application rate). A refined assessment was conducted to further characterize the risk. The application rate (or the rate at which the non-target plants will be exposed) was determined by taking into account the percent drift that will result depending on the application method. Refined risk quotients were re-calculated using EECs corrected for maximum drift with a medium spray droplet size based on the ASAE classification (6% drift deposition for ground application and 23% for aerial application). Using this spray drift exposure scenario, the refined risk quotients did not exceed the level of concern. Thus, metconazole is not expected to pose a risk to non-target terrestrial plants in terrestrial habitats adjacent to a metconazole treatment area when spray drift is taken into account. However, due to the uncertainty of effects at the seasonal maximum application rate (tests were conducted at only the one-time application rate), and due to the existence of toxic effects at the one-time application rate, a precautionary label statement and terrestrial spray buffer zones are required.

To address the potential sensitivity of terrestrial habitats to exposure of metconazole, terrestrial spray buffer zones were determined based on crop application rates and method of application (ground or aerial). For ground application, required spray buffer zones are zero to one metre, and for aerial application, required spray buffer zones are zero to 15 m. Details on the required size of the terrestrial buffer zones are provide on the Caramba Fungicide label and in Appendix I, Table 25.

4.2.2 Effects on Aquatic Organisms

Although the use pattern of metconazole does not include direct application to water, the possibility that aquatic systems will be exposed to metconazole directly or indirectly, cannot be ruled out. Metconazole may enter the aquatic environment through spray drift and/or run-off. Also, pesticides that are bound to soil particles may enter aquatic environments through soil erosion. Since metconazole has a tendency to adsorb to soil, this route of exposure may potentially be a source of contamination of aquatic environments.

The risk to freshwater organisms was based upon the use pattern for the end-use product, Caramba Fungicide, and the evaluation of ecotoxicity data for the following organisms:

- One freshwater invertebrate species; daphnid (acute and chronic studies);
- Two fish species representing freshwater vertebrates (acute and chronic exposure for juveniles, and early life-stage exposure studies);
- One green algae, one diatom and one aquatic vascular plant species.

The risk to estuarine/marine aquatic organisms was based upon the use pattern for the end-use product, Caramba Fungicide, and the evaluation of ecotoxicity data for the following organisms:

- Two estuarine/marine invertebrates; mysid shrimp (acute and chronic studies), and eastern oyster (acute study);
- One marine fish species representing marine vertebrates (acute study);
- One marine diatom (acute study).

The ecological risk assessment of metconazole to aquatic organisms was conducted by first evaluating the ecotoxicity data to determine the most sensitive ecotoxicity endpoints (Appendix I, Table 17). These values were then incorporated into the deterministic risk quotient for the screening level risk assessment (Appendix I, Table 20).

In those cases where the screening level assessments resulted in the level of concern being exceeded, a refined assessment was conducted in order to further characterize the risk to aquatic organisms (Appendix I, Table 22 and Table 23). Whereas the screening level assessment assumes a direct overspray to a water body, the refined assessment identifies the risk from drift and runoff exposure in freshwater and marine ecosystems.

The proposed use of metconazole is not expected to pose a risk to freshwater invertebrates. The results of the acute daphnid study showed moderate toxicity (48-hour LC_{50} of 4.2 mg a.i./L), and the chronic study showed effects on mortality (LC_{50} of 1.5 mg a.i./L) and reproduction (NOEC of 0.16 mg a.i./L). Screening level risk quotients were calculated by incorporating these toxicity endpoints along with the assumption of direct exposure of an aquatic habitat to the proposed seasonal maximum application rate of 225 g a.i./ha. The level of concern for daphnids resulting from metconazole exposure was not exceeded on both an acute and chronic basis.

The proposed use of metconazole is not expected to pose a risk to the juvenile life stages of freshwater fish. The results of the acute freshwater fish studies showed moderate toxicity (48-hour LC_{50} of 2.2 mg a.i./L for rainbow trout and 3.9 mg a.i./L fathead minnow), and the chronic rainbow trout study showed effects on mortality and sublethal effects (LC_{50} of 1.69 mg a.i./L, and NOEC of 0.91 mg a.i./L). Risk quotients calculated at the screening level, incorporating the proposed seasonal maximum application rate, did not exceed the level of concern for freshwater fish on both an acute and chronic basis.

The early life stages (ELS) of freshwater fish may be affected by the use of metconazole. The most sensitive NOEC for rainbow trout ELS was 0.0029 mg a.i./L (for body measurements and mortality). Screening level risk quotients exceeded the level of concern, thus triggering label statements, and the requirement of spray buffer zones to protect sensitive freshwater habitats. A refined risk assessment was conducted to further characterize the risk of metconazole to aquatic habitats adjacent to a potential treatment area. Refined risk quotients for metconazole exposure via spray drift and run-off were determined. Once spray drift was taken into account (refined for a medium spray quality for both ground and aerial application), the refined risk quotient values decreased to below the level of concern for drift. However, results of aquatic ecoscenario modelling indicated that the level of concern resulting from metconazole run-off is exceeded for the early life stages of fish. Thus, metconazole run-off may pose a risk to early life stages of fish dwelling in aquatic habitats adjacent to potential treatment areas.

The proposed use of metconazole is not expected to pose a risk to freshwater algae. For the green alga (*Pseudokirchneriella subcapitata*), the most sensitive NOEC and EC_{50} values were 0.062 mg a.i./L and 0.20 mg a.i./L, respectively. For the freshwater diatom (*Navicula pelliculosa*), the most sensitive NOEC and EC_{50} values were 0.031 mg a.i./L and 0.097 mg a.i./L, respectively. Based on the calculated screening level risk quotients, the level of concern for freshwater algae is not exceeded.

Duckweed (*Lemna gibba*) is sensitive to metconazole based on direct exposure. NOEC and EC50 values of 0.00051 mg a.i./L and 0.025 mg a.i./L resulted in screening level risk quotients exceeding the level of concern for aquatic vascular plants, thus triggering label statements and the requirement of spray buffer zones to protect sensitive freshwater habitats. A refined assessment was conducted to further characterize the risk. Once spray drift was taken into account (refined for a medium spray quality for both ground and aerial application), the refined risk quotient values decreased to below the level of concern. However, results of aquatic ecoscenario modelling indicated that the level of concern resulting from metconazole run-off is exceeded. Thus, metconazole run-off may pose a risk to aquatic vascular plants located in aquatic habitats adjacent to potential treatment areas.

The proposed use of metconazole is not expected to pose a risk to estuarine and marine organisms including invertebrates, fish and algae. The toxicity endpoint values were: an LC50 of 0.75 mg a.i./L (acute mortality for mysid shrimp); NOEC of 0.024 mg a.i./L (chronic reproductive effects for mysid shrimp); EC50 of 2.3 mg a.i./L (acute shell deposition for eastern oyster); LC50 of 6.3 mg a.i./L (acute mortality for sheepshead minnow) and EC50 of 1.7 mg a.i./L (acute cell density inhibition for the marine diatom, *Skeletonema costatum*). Using these toxicity endpoint values along with the proposed maximum seasonal application rate of metconazole (225 g a.i./ha) to calculate screening level risk quotients, the level of concern was not exceeded for these organisms.

No studies were submitted to assess the acute or chronic toxicity of metconazole to amphibians. Thus, the most sensitive toxicity endpoint values from fish toxicity studies were used as surrogate data for in-water life-stages. Screening level risk quotients were calculated assuming direct application of 225 g a.i./ha to a shallow, seasonal water body (15 cm deep), and it was determined that the level of concern for amphibians is not exceeded on an acute basis; however, it is exceeded on a chronic basis. Thus, a refined assessment was conducted to further characterize this chronic risk. When the spray drift scenario is refined for a medium spray quality for ground and aerial application, the level of concern is still exceeded for amphibians. Results of aquatic ecoscenario modelling also indicate that the level of concern from exposure to metconazole run-off is exceeded. Thus, metconazole drift and metconazole run-off may pose a risk to amphibians dwelling in aquatic habitats adjacent to potential treatment areas.

To address the potential sensitivity of amphibians, early life stages of freshwater fish, and aquatic vascular plants to exposure of metconazole; aquatic spray buffer zones were determined based on crop application rates and method of application (ground or aerial). For ground application, required aquatic buffer zones are zero to two metres; and for aerial application, required aquatic spray buffer zones are zero to 50 m. Details on the size of the required freshwater and marine spray buffer zones are provided on the Caramba Fungicide label and in Appendix I, Table 25.

No studies were submitted for sediment dwelling invertebrates. Due to the adsorption and persistence of metconazole in sediment, and the observed toxicity to daphnids, these data are required and currently constitute a data deficiency.

The early-life stage of fish was determined to be the most sensitive freshwater organism. Due to the persistence of metconazole in various environmental media, its effects on reproduction of several non-target species including mammals, birds, and aquatic organisms, and the exceedence of risk for amphibians even after the refined risk assessment for run-off and drift, further ecotoxicity data are required. Thus, a full life cycle toxicity test for freshwater fish is required for further refinement of the risk to aquatic organisms. As these data were not submitted, this currently constitutes a data deficiency.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Wheat

Control of septoria leaf blotch (*Septoria tritici*): Results from four efficacy trials demonstrated that application of Caramba Fungicide at 45 or 60 g a.i./ha (0.5 - 0.7 L product/ha) under high disease pressure provided an average of 79.5 and 84.5% reduction of septoria leaf spot caused by *S. tritici*, respectively, compared to the untreated control.

Control of leaf rust (*Puccinia recondita*): Results of three efficacy trials for control of leaf rust on wheat demonstrated that Caramba Fungicide applied once at 45 or 60 g a.i./ha (0.5 and 0.7 L product/ha) under low disease pressure provided an average of 93.6 and 91.5% control of leaf rust, respectively, compared to the untreated control. It is expected that under high disease pressure, Caramba Fungicide should perform at least as well as the commercial standards tested.

Control of tan spot (*Pyrenophora tritici-repentis*): Results from three efficacy trials demonstrated that Caramba Fungicide applied once at 45 or 60 g a.i./ha (0.5 and 0.7 L product/ha) under low disease pressure provided an average of 70 and 74.4% control of tan spot, respectively, compared to the untreated control. It is expected that under high disease pressure, Caramba Fungicide should perform at least as well as the registered commercial standards.

5.1.2 Wheat, Barley, Oats and Rye

Suppression of fusarium head blight (*Fusarium graminearum;* FHB): Results from ten efficacy trials (seven on wheat and three on barley) demonstrated that Caramba Fungicide applied at 90 g a.i./ha (1 L product/ha) consistently suppressed Fusarium head blight on wheat and barley. Caramba Fungicide provided 30.6 and 40.3% reduction (average of six trials) of disease severity on wheat and 40.6 and 52.3% control of FHB on barley compared to the untreated control, which is consistent with disease suppression. All treatments provided between 25 and 83% reduction of deoxynivalenol in the harvested grain and increased yield when compared to the untreated control.

5.1.3 Soybeans

Control of Asian soybean rust (*Phakopsora pachyrhizi*): Ten efficacy and two tolerance trials conducted in Unites States, Paraguay, South Africa and Zimbabwe were submitted for review. In Florida, Caramba Fungicide applied two times at either 54 or 63 g a.i./ha (0.6 - 0.7 L product/ha) provided 42.5 - 100% disease control of Asian soybean rust compared to the untreated control under moderate to high disease pressure. In Georgia, results of trials showed that 63 g a.i./ha (0.7 L product/ha) of Caramba Fungicide with a non-ionic surfactant (AgSurf or Agral 90 at 0.25%) applied twice with a 14 day interval under moderate to high disease pressure provided good control of Asian soybean rust compared to the untreated control. Disease severity was reduced in the early evaluation (31.3 - 70% of control) and maintained in the late evaluation. In Louisiana and Paraguay, Caramba Fungicide applied twice at 54 g a.i./ha (0.6 L product/ha) under high disease pressure with 21 to 28 day interval provided 52.1% control of Asian soybean rust, compared to the untreated control. When applied under low disease pressure, Caramba Fungicide at 54 g a.i./ha provided 89.1% control of Asian soybean rust, compared to the untreated control. In the South Africa and Zimbabwe trials, the Area Under the Disease Progress Curve, which represents the culmination of Asian soybean rust severity over time, was nearly 73% lower than in the untreated control when Caramba Fungicide was applied three times at 54 g a.i./ha (0.6 L product/ha) with a 20 day interval. The proposed 10 day interval was not tested, however, since Caramba Fungicide provided good level control of Asian soybean rust when applied at 14 day intervals, it should also performed as well or better with 10-day interval. No phytotoxicity effects are expected with 10-day interval.

5.1.4 Sugar Beets

Control of cercospora leaf spot (*Cercospora beticola*): Results from seven efficacy trials demonstrated that Caramba Fungicide provided good control of cercospora leaf spot compared to the untreated control. Percent control for Caramba Fungicide at the high proposed rate of 112 g a.i./ha (1.25 L product/ha) varied from 31.3 - 96.4% under low disease pressure and from 50 - 67% under moderate to high disease pressure. The lowest applied rate of 90 g a.i./ha (1 L product/ha) provided 86 - 98% control of cercospora leaf spot compared to the untreated control. The results of trials where Caramba Fungicide was applied in combination with other fungicides as a tank-mix or in rotation were not reviewed since efficacy of Caramba Fungicide cannot be assessed in these trials. However, these trials showed that Caramba Fungicide can be used in combination with other registered products for resistance management as indicated on the proposed product label.

5.1.5 Aerial application

It was proposed that Caramba Fungicide be applied by air at rates listed in the application rate and timing tables (crop specific) in a minimum water volume of 50 L/ha. However, the submitted data for ground application did not test the water spray volume of 50 L/ha. The following rationale was provided to support the aerial application: (i) metconazole is registered as aerial application in Brazil on bananas; (ii) metconazole and tebuconazole are from similar groups (triazole fungicides); (iii) tebuconazole (Folicur) is registered for FHB suppression and leaf disease control by aerial applications; (iv) it is not expected that low water volume or aerial application will negatively affect metconazole efficacy. Moreover, efficacy trials comparing high water volume with low water volume application (50 L) are ongoing. Based on the rationale provided by the applicant, aerial application is conditionally supported. Confirmatory efficacy trials should be submitted to demonstrate that the proposed aerial application will not negatively affect metconazole efficacy.

5.2 Phytotoxicity to Host Plants

No phytotoxicity was attributed to Caramba Fungicide in trials with small grains (spring and winter wheat, barley). Caramba Fungicide has the potential to cause foliar chlorosis in soybeans, however, this condition is generally associated with soybeans that are highly stressed from drought, heat, and ground compaction. These environmental conditions are not as pronounced in

Canada as they are in southern United States and growers are unlikely to spray a fungicide when the risk of disease development is low. There were no observations of sugar beet phytotoxicity of any kind in any of the trials.

5.3 Impact on Succeeding Crops

Data on the impact of Caramba Fungicide on succeeding crops were not submitted for review.

5.4 Economics

No market analysis was done for Caramba Fungicide.

5.5 Sustainability

5.5.1 Survey of Alternatives

The chemical fungicides listed in Table 5.5.1 are registered for control or suppression of diseases of wheat, barley, oats, rye, soybeans and sugarbeets found on the Caramba Fungicide label.

Table 5.5.1 Alternative active ingredients registered for control or suppression of disease claims on the Caramba Fungicide accepted label.

Crop	Disease Claim	Technical Grade Active Ingredient
Wheat	septoria leaf spot (*Septoria tritici* and *Stagonospora nodorum*)	difenocanazole, metalaxyl-m, propiconazole, prothioconazole, tebuconazole, pyraclostrobin, mancozeb, trifloxystrobin
	tan spot (*Pyrenophora tritici-repentis*)	propiconazole, prothioconazole, tebuconazole, pyraclostrobin, mancozeb
	leaf rust (*Puccinia recondita*)	propiconazole, tebuconazole, pyraclostrobin, mancozeb, trifloxystrobin
Barley, oats, rye and wheat	fusarium head blight (*Fusarium graminearum*)	prothioconazole, tebuconazole
Soybeans	Asian soybean rust (*Phakopsora pachyrhizi*)	azoxystrobin, propiconazole, pyraclostrobin
Sugarbeet	cercospora leaf spot (*Cercospora beticola*)	propiconazole, pyraclostrobin, metiram

5.5.2 Compatibility with Current Management Practices Including Integrated Pest Management

As a broad-spectrum fungicide, metconazole is an important tool that can be integrated into an IPM program alongside the use of resistant varieties, cultural controls and disease prediction models.

5.5.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Metconazole, being a member of the triazole (SBI/DMI) group of fungicides, represents a moderate risk for resistance development. The risk does vary, however, depending on a number of inherent factors related to the individual pathogens and the agronomic practices under which they are grown. Following the recommendations made by the Fungicide Resistance Action Committee for several important crops, appropriate resistance management strategies for the triazoles should be based mainly on mixtures, alternations and reductions in the number of applications. To limit the potential for development of resistance, metconazol or other Group 3 fungicides should not be applied more than two times per season.

5.5.4 Contribution to Risk Reduction and Sustainability

No information about contribution to risk reduction and sustainability were provided.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e., persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, metconazole and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[4] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Metconazole does not meet all Track 1 criteria, nor does it form any transformation products that meet all Track 1 criteria, and therefore is not considered a Track 1 substance. See Appendix I, Table 24, for comparison with Track 1 criteria.

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[4] DIR99-03, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[5]. The list is used as described in the PMRA Notice of Intent NOI2005-01[6] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[7], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade metconazole does not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.
- The end-use product Caramba Fungicide does not contain any formulants of health or environmental concern identified in the *Canada Gazette*. However, the end-use product does contain an aromatic petroleum distillate. Therefore, the label for the end-use product Caramba Fungicide will include the statement: "This product contains aromatic petroleum distillates that are toxic to aquatic organisms."

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-024.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for metconazole is adequate to define the majority of toxic effects that may result from exposure to metconazole. In short- and long-term toxicology studies on laboratory animals, target organs were the liver, adrenals, reproductive organs and haematopoeitic systems. In dogs, the eye is also a target. Metconazole shows durational effects in all species. In mice, tumours were seen in the liver of both males and females only at excessively high doses; however, male mice exhibited skin sarcomas at the lowest dose tested. There was no evidence of genotoxicity. When administered to pregnant rabbits, craniofacial malformations were observed at doses that did not elicit maternal toxicity, and in rats, spinal malformations were only observed at maternally toxic doses.

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[5] *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

[6] NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

[7] DIR2006-02, PMRA Formulants Policy.

Mixers, loaders, applicators handling Caramba Fungicide and workers re-entering treated fields of cereals, soybeans or sugar beets are not expected to be exposed to levels of metconazole that will result in unacceptable risk when Caramba Fungicide is used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

The nature of the residue in plants and animals is adequately understood. The residue definition in plants for enforcement purposes is defined as the sum of *cis*- and *trans*-metconazole. The residue definition in all primary and rotational crops, except barley, oats, rye and wheat for risk assessment purposes is defined as the sum of *cis*- and *trans*-metconazole. The residue definition in all primary and rotational crops of barley, oats, rye and wheat for risk assessment purposes is defined as the sum of *cis*- and *trans*-metconazole as well as M11. The residue definition in animals for enforcement purposes is defined as the sum of *cis*- and *trans*-metconazole. The residue definition in animal matrices for risk assessment purposes is defined as the sum of *cis*- and *trans*-metconazole as well as M12, M1 and M31 and their aglycones. The proposed use of metconazole on barley, oats, rye, wheat, soybeans and sugar beets does not constitute an unacceptable risk (acute, chronic or cancer) to any segment of the population, including infants, children, adults and seniors. Crop residue data have been reviewed to recommend maximum residue limits (Table 3.5.1).

7.2 Environmental Risk

There are no concerns regarding the proposed use of metconazole affecting terrestrial invertebrates including earthworms and honeybees, or terrestrial vertebrates including birds and small wild mammals. However, adverse effects were observed on terrestrial plants. Risk mitigation for terrestrial vertebrates includes precautionary label statements of metconazole toxicity. In addition, risk mitigation for non-target terrestrial plants also includes the requirement of spray buffer zones up to one metre in size for ground application and up to 15 m in size for aerial application.

There are no major concerns regarding the proposed use of metconazole affecting freshwater invertebrates (such as daphnids) and marine invertebrates (such as mysid shrimps and molluscs), juvenile stages of freshwater fish, freshwater algae, marine fish and marine algae. However, effects were observed on early life stages of freshwater fish and freshwater aquatic vascular plants. Given persistence and partitioning concerns, additional toxicity data are required. Risk mitigation for sensitive aquatic organisms includes precautionary label statements of metconazole toxicity. In addition, risk mitigation for non-target aquatic organisms also includes the requirement of spray buffer zones up to two metre in size for ground application and up to 50 m in size for aerial application.

In order to further characterize the risk to aquatic organisms, three ecotoxicity studies are being requested: acute exposure and chronic exposure of chironomids to metconazole, and a full life cycle toxicity test (i.e. egg to egg) for all life stages of fish.

7.3 Value

Based on the information provided, the following claims can be supported:

- Suppression of fusarium head blight (*Fusarium graminearum)* on wheat and barley when Caramba Fungicide is applied once at 90 g a.i./ha (1.0 L product/ha). This claim can be extrapolated to oats and rye, since FHB can also affect these crops;

- Control of septoria leaf spot *(Septoria tritici*) on wheat when Caramba Fungicide is applied once at 45 to 60 g a.i./ha (0.5 to 0.7 L product/ha). Control of *Stagonospora nodorum* can also be supported, as *S. tritici* is often found as part of leaf spot complex with *S. nodorum*;

- Control of tan spot (*Pyrenophora tritici-repentis*) on wheat when Caramba Fungicide is applied once at 45 to 60 g a.i./ha (0.5 to 0.7 L product/ha);

- Control of leaf rust (*Puccinia recondita*) on wheat when Caramba Fungicide is applied once at 45 to 60 g a.i./ha (0.5 to 0.7 L product/ha);

- Control of Asian soybean rust (*Phakopsora pachyrhizi*) on soybeans when Caramba Fungicide is applied at 63 g a.i./ha (0.7 L product/ha) up to two times at a 10 to 21 day interval. Use the shorter interval when rust pressure is high;

- Control of cercospora leaf spot (*Cercospora beticola*) on sugar beets when Caramba Fungicide is applied up to two times at 1.1 to 1.25 L/ha (90 to 112 g a.i./ha) on a 14 day interval.

- Based on the rationale provided by the applicant, the proposed aerial application for Caramba Fungicide on cereals, soybeans and sugar beets is conditionally supported. Confirmatory efficacy trials should be submitted to demonstrate that the proposed aerial application will not negatively affect metconazole efficacy.

7.4 Unsupported Uses

All uses were supported.

8.0 Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of Metconazole Fungicide Technical and Caramba Fungicide, containing the technical grade active ingredient metconazole, to control a variety of fungal diseases on barley, oats, rye, wheat, soybeans and sugar beets.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been found acceptable when all risk-reduction measures are followed, as a condition of these registrations, additional scientific information is being requested from the applicant. For more details, refer to the Section 12 Notice associated with these conditional registrations. The applicant will be required to submit this information within the time frames indicated below.

NOTE: The PMRA will publish a consultation document at the time when there is a proposed decision on applications to convert these conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

Human Health

- The applicant is required to submit a modified plant analytical method for D0508 that reflects the recommendation of the ILV laboratory and is reviewed by the applicant's quality assurance unit. Additionally, the applicant must provide a confirmatory method either by modifying the method to provide information on a second MS/MS ion transition or an alternate chromatographic system and provide the required information to demonstrate the extraction efficiency of the method.

- The applicant is required to submit a validated animal enforcement method.

- Metconazole must be tested through a valid and appropriate multiresidue method.

- Rotational crop studies are considered conditionally acceptable pending the submission of acceptable freezer storage stability data for M11 in wheat forage stored frozen for up to 21 months, as well as, for *cis*- and *trans*-metconazole in wheat grain and straw stored frozen for up to 18 months, in wheat forage and radish tops stored frozen for up to 21 months, and in lettuce stored frozen for up to 19 months.

- Confirmatory crop field trials for barley, oats, rye and wheat conducted at the Canadian rate of 90 g a.i./ha in Canadian representative growing regions are required. For barley, five field trials conducted in NAFTA Region 14 are required. For oats, four field trials conducted in NAFTA Region 14 are required. For rye, one field trial conducted in NAFTA Region 7 and two field trials conducted in NAFTA Region 14 are required. For wheat, two field trials conducted in NAFTA Region 7, one field trial conducted in NAFTA Region 7A and three field trials conducted in NAFTA Region 14 are required.

Environment

- Non-target freshwater invertebrate study: Acute and chronic ecotoxicity study exposing invertebrates to metconazole.

- Fish full-life cycle toxicity test: Chronic ecotoxicity study exposing all life stages of fish to metconazole.

Value

To support aerial application, at least three confirmatory trials are required on one of the crop/pest combinations listed on the Caramba Fungicide label (i.e., barley/FHB, wheat/FHB, sugarbeets/cercospora leaf spot, etc.) comparing the efficacy of Caramba Fungicide when applied with high water volume (a minimum of 100 L of water per ha) versus low water volume (50 L of water per ha).

List of Abbreviations

µg	microgram(s)
µL	microlitre(s)
A	applicator
abs	absolute
a.i.	active ingredient
AD	administered dose
ADI	acceptable daily intake
adj	adjusted
A/G	Albumin/Globulin ratio
ALK	alkaline phosphatase
APTT	activated partial thromboplastin time
ARfD	acute reference dose
ASAE	American Society of Agricultural and Biological Engineers
atm	atmosphere(s)
ATPD	area treated per day
AUDPC	area under disease progress curve
BAF	bioaccumulation factor
BCF	bioconcentration factor
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
Chal	challenge
Ci	curies
cm	centimetre(s)
cm^2	centimetre(s) squared
CML	closed mixing/loading systems
col	cholesterol
Crt	control
CT	crop treated
DAT	day(s) after treatment
DFR	dislodgeable foliar residue
DM	dry matter
DMI	de-methylation inhibitor
DNA	deoxyribonucleic acid
dpm	disintegrations per minute
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in the test population)
DT_{90}	dissipation time 90% (the dose required to observe a 75% decline in the test population)
dw	dry weight
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EDE	estimated daily exposure

EEC	estimated environmental concentration
ELS	early life stage
E/P	concentration ratio of 17í-estradiol to progesterone (E/P ratio)
EPA	Environmental Protection Agency
ER_{50}	effective rate for 50% of the population
$F_0/F_1/F_2$	Parental/First offspring generation/Second offspring generation
fc	food consumption
FDA	*Food and Drugs Act*
FHB	Fusarium head blight
g	gram(s)
GAP	good agricultural practice
GB	groundboom
GBq	gigabecquerel(s)
GC	gas chromatography
GD	gestation day
gen	general
GGT	Gamma glutamyl transferase
GI	gastrointestinal
GLC	gas-liquid chromatography
ha	hectare(s)
HAFT	highest average field trial
HDPE	high-density polyethylene
HPLC	high performance liquid chromatography
hr	hour(s)
HR_5	hazardous rate 5%
ID	identification
ILV	independent laboratory validation
inc	increased
int	interim sacrifice
IPM	Integrated Pest Management
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
*K*oc	organic-carbon partition coefficient
*K*ow	*n*–octanol-water partition coefficient
L	litre(s)
LADD	lifetime average daily dose
LC	liquid chromatography
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
m	metre(s)
m^3	metre(s) cubed
max.	maximum
mg	milligram(s)

mL	millilitre(s)
MAS	maximum average score
min.	minimum
MIS	maximum irritation score
M/L/A	Mixer/loader/applicator
MOE	margin of exposure
MRBD	Maximum Reasonably Balanced Diet
MRL	maximum residue limit
MRM	multiple reaction monitoring
MS	mass spectrometry
MTD	maximum tolerated dose
m/z	mass to charge ratio
n	number
N/A	not applicable
NAFTA	North American Free Trade Agreement
nm	nanometre(s)
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NPD	nitrogen phosphorus detector
NZW	New Zealand white
OP	open pour
Pa	Pascal(s)
PBI	plantback interval
PCNA-positive	Proliferating cell nuclear antigen (PCNA)-positive
PCPA	*Pest Control Product Act*
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppb	parts per billion
ppm	parts per million
Q_1*	cancer potency factor
R/A	risk assessment
REI	Restricted entry interval
rel	relative
RfD	reference dose
RQ	risk quotient
SSD	species sensitivity distribution
TA	triazolylalanine
TAA	triazolylacetic acid
ter	terminal sacrifice
TGAI	technical grade active ingredient
TP	transformation product
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
TWA	Time-weighted average

UDS	unscheduled DNA synthesis
US	United States
UV	ultraviolet
wt	weight
yr(s)	year(s)

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ (ppm)	Matrix	Reference
Plant						
Plants	D0508	*cis-* and *trans-* metconazole M21, M11, M30 1,2,4-T, TA, TAA	LC/MS/MS	0.005 each isomer 0.01 0.05	wheat grain, wheat straw, soybean seed, soybean hay, sugar beet root, sugar beet tops, wheat flour, soybean oil, sugar beet juice and sugar beet molasses	1403153 1403157
Banana	M2722	*cis-* and *trans-* metconazole	GC/NPD	0.05 each isomer	whole banana, banana pulp, banana peel	1408094 1408095
Plants	555/0	*cis-* and *trans-* metconazole	LC/MS/MS	0.005 each isomer	wheat forage, grain and straw, canola seed, lemon fruit, pea seed, tomato fruit	1590332
Cereals	FAMS 050-01	*cis-* and *trans-* metconazole	GC/MS or GC/NPD	0.01 each isomer (grain) 0.03 each isomer (straw)	wheat grain and straw	1590331
Plant, animal, soil	MRM DFG Method S19	*cis-* and *trans-* metconazole	GC/MS	0.01 each isomer	grapes, peas, wheat grain, rapeseed, fat, milk, meat, eggs and soil	1403156 1403161
Animal						
Dairy	RM-41M-1	*cis-* and *trans-* metconazole	GC/NPD or LC/MS/MS	0.02 each isomer 0.04 each isomer	milk, skim milk cream	1400587
Tissue	RM-41M-2	*cis-* and *trans-* metconazole	LC/MS/MS	0.02 each isomer	fat, kidney, muscle and liver	1400587
Tissue	RM-4 1M-3	M1 and M12	LC/MS/MS	0.02 each isomer	fat, kidney, muscle and liver	1400587
Soil						
Soil	D0506	Metconazole-cis isomer	HPLC-MS/MS m/z 320 to 70.1	10 ppb		1396931
		Metconazole-trans isomer				
		M11	HPLC-MS/MS m/z 336.1 to 125.1			
		M21				

Matrix	Method ID	Analyte	Method Type	LOQ (ppm)	Matrix	Reference
		M30	HPLC-MS/MS m/z 334.1 to 111.1			
		Triazol	HPLC-MS/MS m/z 70.5 to 43			
Sediment						
Sediment	HUK 579/121-01R	Metconazole	GLC-NPD	1.2 ppb		1396932
Water						
	FAMS 058-01	Metconazole-cis isomer	GLC-NPD	0.05 ppb		1560749
		Metconazole-trans isomer				

MRM = multiresidue method

Table 2 Acute Toxicity of Metconazole and Its Associated End-use Product (Caramba Fungicide)

Study Type	Species	Result	Comment	Reference
Acute Toxicity of Metconazole (Technical)				
Oral	Fischer 344 rat	♂ LD_{50} = 727 mg/kg bw ♀ LD_{50} = 595 mg/kg bw Combined LD_{50} = 660 mg/kg bw	Moderate Toxicity	1405589
Oral	Crl: CD-1 (ICR) BR mouse	♂ LD_{50} = 718 mg/kg bw ♀ LD_{50} = 410 mg/kg bw Combined LD_{50} = 566 mg/kg bw	High Toxicity	1405589
Dermal	Fischer 344 rat	Combined LD_{50} > 2000 mg/kg bw	Low Toxicity	1405589
Dermal	New Zealand White rabbit	Combined LD_{50} > 2000 mg/kg bw	Low Toxicity	1405589
Inhalation	Crl:CD(SD)BR rat	Combined LC_{50} > 5.588 mg/L	Low Toxicity	1405591
Skin irritation	New Zealand White rabbit	MAS (24 – 72hours) 0/8	No label comments	1405592
Eye irritation	New Zealand White rabbit	MIS (24 hours) 12.8/110 MAS (4, 23, 48 hours) 9.4/110 at 72 hours	WARNING – EYE IRRITANT	1405592
Skin sensitization	Dunkin-Hartley guinea pig	unvalidated study	POTENTIAL SKIN SENSITIZER	1405592
Acute Toxicity of End-Use Product - Caramba				
Oral	Crl:CD®(SD)BR rat	♂ LD_{50} = 3526 mg/kg bw ♀ LD_{50} = 2102 mg/kg bw	Low Toxicity	1403132
Dermal	Crl:CD®(SD)BR rat	Combined LD_{50} > 4000 mg/kg bw	Low Toxicity	1403134

Study Type	Species	Result	Comment	Reference
Inhalation	Crl:CD®(SD)BR rat	♂ LD_{50} = 4.951 mg/L ♀ LD_{50} = 5.563 mg/L	Low Toxicity	1403136
Skin irritation	New Zealand White rabbit	MAS (24, 48, 72 hours) 0.33/8 MIS (1 hour) 1/8	No label comment required	1403142
Eye irritation	New Zeland White rabbit	MAS (24, 48, 72 hours) 21.1/110 MIS (48 hours) 21.7/110 Persistence past 7 days	WARNING – EYE IRRITANT	1403140
Skin sensitization	Guinea pig	Chal = 2/20; Crt = 2/10	No label comment required	1403144

[a] MAS = maximum average score for time periods noted

[b] MIS = maximum irritation score

Table 3 Toxicity Profile of Technical Metconazole

Study Type	Species	Results[a] (mg/kg/day in M/F)	Reference
21-day dermal	Fischer 344 rat (10/sex/dose)	NOAEL: 500 mg/kg bw/day in females and 1000 mg/kg bw/day in males LOAEL: 1000 mg/kg bw/day in females **1000 mg/kg bw/day:** ↑ APTTs (♀) ↑ GGT, blood chol and blood urea nitrogen (♀); ↑ abs and rel liver wts (♀)	1405601
28-day dietary	Fischer 344 rat (7/sex/dose)	NOAEL: 30 ppm/2.73 mg/kg bw/day in males; 100 ppm/10.12 mg/kg bw/day in females LOAEL: 100 ppm/9.12 mg/kg bw/day in males; 1000 ppm/ 97.05 mg/kg bw/day in females **≥ 100 ppm:** ↓ bw at end of wks 1 (6.1%) and 3 (6.4%) (♂) **≥ 1000 ppm:** ↑ GGT, ↓ chol (♂♀);↑ adj liver wt (♂♀) and ↑ rel liver wt (♀); ↑ enlargement, pallor and diffuse fatty vacuolation (♂♀ - with ↑ severity in both); ↑ centrilobular parenchymal hypertrophy (♀) ↑ adj spleen wts (♀)	1405599
28-day dietary	Beagle dog (2/sex/dose)	NOAEL: 100 ppm/2.5 mg/kg bw/day in females; 1000 ppm/ 25 mg/kg bw/day in males LOAEL: 1000 ppm/25 mg/kg bw/day in females; 7000 ppm/175 mg/kg bw/day in males **≥ 1000 ppm:** ↑ APTTs (♀) ↑ thyroid wts (♀) **≥ 7000 ppm:** ↓ bw (24.27 ♂), bwg (281.43/256.6% ♂♀), fc (♂♀),	1405600

Study Type	Species	Results[a] (mg/kg/day in M/F)	Reference
		↑ platelets and APTTs (♂♀); ↑ rel spleen wts (♂); ↑ rel liver wts (♂); ↑ ALK and A/G ratios (♂♀) ↑ rel heart wts (♂); ↑ rel testes wts (♂)	
90-day dietary	Crl:CD-1(ICR)BR mice (12/sex/dose)	NOAEL: 30 ppm (4.6/6.4 mg/kg bw/day) LOAEL: 300 ppm (50.5/60.7 mg/kg bw/day) **≥ 300 ppm:** ↓ body weight (5.1 ♂); ↓ chol (♂♀); ↓ bilirubin (♂); ↑ creatinine (♂); ↑ liver wt (♂/♀); ↑ hepatcellular hypertrophy and vacuolation (with inc↑ severity) (♂♀); ↑ spleen wt (♀); lymphoid hyperplasia in spleen (with inc↑ severity ♂)	1405596
90-day dietary	(SPF) Fischer 344 rats (10/sex/dose with 20 control and satellite groups with 6 week recovery)	NOAEL: 100 ppm (6.40 mg/kg bw/day) in males; 300 ppm (22.06 mg/kg bw/day) in females LOAEL: 300 ppm (19.17 mg/kg bw/day) in males; 1000 ppm (71.42 mg/kg bw/day) in females Incomplete recovery **≥ 300 ppm:** ↑ pallor, fatty vacuolation and centrilobular hypertrophy (♂); **≥ 1000 ppm:** ↑ food spillage (♀);↓ fc in wk 13 (♀); ↑ GGT (♀); ↑ pallor of liver and thickening (♀); ↑ exaggerated lobular patterns and enlargement (♂♀);↑ fatty vacuolation of liver (♀) ↑ moderate cortical vacuolation of adrenals (♂)	1405595
90-day dietary	Beagle dog (5/sex/dose)	NOAEL: 60 ppm (1.5 mg/kg bw/day) LOAEL: 600 ppm (15mg/kg bw/day) **≥ 600 ppm:** ↓ bwg (28.76%) and fc (♀) ↑ platelet counts (♂) ↑ rel thyroid wt (♀) ↑ congestion/haemorrhage and cystitis in urinary bladder (♀)	1405597
1-year dietary	Beagle dog (4/sex/dose)	NOAEL: 300 ppm (12.07/10.49 mg/kg bw/day) LOAEL: 1000 ppm (39.0/36.80 mg/kg bw/day) **≥ 1000 ppm:** ↑ ALK (♂♀); hepatocyte vacuolation (♀), ↑ Kuppfer cell pigmentation (♀) ↑ red foci in the stomach (♂); ↑ congestion/haemorrhages in caecum (♀)	1405598

Study Type	Species	Results[a] (mg/kg/day in M/F)	Reference
Carcinogenicity (18-month dietary)	Crl:CD-1(ICR)BR mice (51+12/sex/dose – 12 animals/sex/dose used for interim sac at wk 52)	NOAEL: undetermined LOAEL: 30 ppm/ 4.4/5.7 mg/kg bw/day **≥ 30 ppm:** ↓ bwg overall (♀) ↑ total leukocyte counts (♂); ↑ total leukocytes, neutrophils and lymphocytes (♀);↓ splenic wts (int ♂); ↓ splenic wts (int ♀); ↓ splenic wts (ter ♀); ↑ atrophy, prominent trabuclae and stroma in spleen (int ♀) ↑ adrenal wts (int ♂); ↑ liver weights (ter ♂); ↑ focal necrosis (ter ♂) ↑ malignant sarcomas in skin (ter ♂)	1405626
Chronic (2-year dietary)	(SPF) Fischer 344 rats (20/sex/dose with 40/sex for control and 10/sex/dose and 20/sex for control as a 12 month interim sac)	NOAEL: 10 ppm/0.44 mg/kg bw/day in males and 100 ppm/5.27 mg/kg bw/day in females LOAEL: 100 ppm/4.29 mg/kg bw/day in males and 300 ppm/15.98 mg/kg bw/day in females MTD not achieved in females **≥ 100 ppm @ 104 wks:** ↑ in cortical vacuolation of adrenal glands (♂) ↑ necrotic inflammatory foci in the liver (♂) **≥ 300 ppm @ 52 wks:** ↓ fc (♂) ↓ platelet counts (♀); ↑ adj liver wts (5.2% ♂); ↑ diffuse pallor and mottled appearance (♂); ↑ monouclear-cell infiltrate (♂/♀ – with inc↑ severity) and centrilobular parenchymal hypertrophy (♂♀); ↑ midzonal macrovesicular lipid vacuolation (– with inc↑ severity ♂) **≥ 300 ppm @ 104 wks:** ↑ spleen wts at 2 yr (♂♀); ↑ basophilic foci/areas of cellular alteration (♂); clear cell foci/areas of cellular alteration in liver (♂)	1405604
Oncogenicity (2-year dietary)	(SPF) Fischer rats (50/sex/dose)	NOAEL: undetermined LOAEL: 100 ppm/4.61/5.51 mg/kg bw/day **≥ 100 ppm:** ↑ eosinophilic foci, centrilobular hypertrophy, pigment deposits in liver (♂) ↑ cortical vacuolation of adrenals (♂♀)	1405613

Study Type	Species	Results^a (mg/kg/day in M/F)	Reference
Two-generation reproduction	Crj:CD (SD)[IGS] rats (24/sex/dose)	**Parental toxicity**: NOAEL: 30 ppm (1.73/2.54 mg/kg bw/day) LOAEL: 150 ppm (8.49/12.88 mg/kg bw/day) **≥ 150 ppm:** ↑ thyroid wts (rel F_0 and rel F_1 ♀) **Offspring toxicity:** NOAEL: 150 ppm (9.05/12.67 mg/kg bw/day) LOAEL: 750 ppm (43.2/63.2 mg/kg bw/day) **750 ppm:** ↓ number pups born live (F_1 and F_2); ↑ number of pups born dead (F_1 and F_2); ↑ number of deaths (F_1 and F_2) and litter size until culling on PND 4 (F_1 and F_2); ↓ mean litter size until end of study with ↓ live birth (F_2) and ↓ viability indices (F_2) single incidence kinked tail (F_1) ↓ bw PND 14 – 21 (F_1 ♀); ↓ bw PND 0 – 21 (♂; ♀ F_2) ↑ abs spleen wt (F_1) and rel spleen wt (F_1 and F_2) ↑ white spots on liver PND 0 – 4 (F_1 and F_2) ↑ dilated renal pelvises PND 5 – 21 (F_2) **Reproductive toxicity:** NOAEL: 30 ppm (1.73/2.51 mg/kg bw/day) LOAEL: 150 ppm (9.05/12.67 mg/kg bw/day) **150 ppm:** ↑ ovary wts (F_1 ♀) (abs and rel ovary wts in F_0 ♀; non-adverse, but pattern of change) ↑ prostate wts F_1	1405632
Developmental / Reproductive toxicity	Crj:CD(SD)[IGS] female rats (24/sex/dose)	**≥ 30 ppm:** ↑ CYP 2B1 (43.5% GD 19) **≥ 150 ppm:** ↑ microsomal protein levels (GD 19) ↑ cytochrome P-450 (GD 19 and 21); ↑ CYP3A2 (GD 19 and 21); ↑ CYP 4A1 (GD 19) **750 ppm:** ↑ CYP 2B1 (GD 21) ↓ bw & bwg throughout treatment; ↓ fc wk 1 and throughout gestation; ↑ hair loss; ↓ terminal bw (11.6% GD 19; 8.6% GD 21) ↑ liver wts (GD 21) ↑ rel ovarian wts (GD 19/21) ↓ corpora lutea (GD21) ↑ PCNA+ cells/PCNA+ corpora lutea (GD 21)	1405635

Study Type	Species	Results[a] (mg/kg/day in M/F)	Reference
		↓ implantations/dam and ↓ live foetuses ↑ resorptions and foetal deaths ↓ 17β-estradiol and E/P ratios (GD 19 and 21 with greater decreases at GD 21 than 19) ↑ progesterone (GD 21)	
Preliminary Developmental toxicity	CD (Sprague-Dawley) rats (6/dose)	**Maternal:** **64 mg/kg bw/day:** ↓ overall bwg (14.63%) and fc in first days of treatment; ↓ gravid uterine wt (5.40%) ↑ late resorptions ↑ post-implantation loss **Developmental:** **≥ 4 mg/kg bw/day:** ↓ foetal bw ♀	1405639
Developmental toxicity	CD (Sprague-Dawley) rats (22/dose)	**Maternal:** NOAEL: 4 mg/kg bw/day LOAEL: 16 mg/kg bw/day **≥ 16 mg/kg bw/day:** ↓ bwg (13.2%); ↑ placental wts **Developmental:** NOAEL: 4 mg/kg bw/day LOAEL: 16 mg/kg bw/day **≥ 16 mg/kg bw/day:** ↑ placental weights ↑ rudimentary/threadlike or agenesis of tails with imperforate anuses	1450640
Preliminary Developmental toxicity	New Zealand White rabbits (6 females/dose/isomer)	***cis:*** **Maternal:** **≥ 10 mg/kg bw/day:** ↑ anorexia and abnormal faeces **Developmental:** **≥ 28 mg/kg bw/day:** ↑ cranial defects and hind limb malformations: domed cranium; absent bilateral hind paw/digits **(-)*cis*:** **Maternal:** **≥ 28 mg/kg bw/day:**	1405643

Study Type	Species	Results[a] (mg/kg/day in M/F)	Reference
		↑ anorexia and abnormal faeces, cold ears ↑ late resorptions **Developmental:** **≥ 28 mg/kg bw/day:** ↑ late resorptions one foetus with cranial defects, sacro-lumbar spina bifida, malrotated hindlimbs ***trans*:** **Maternal:** **≥ 20 mg/kg bw/day:** ↑ anorexia and abnormal faeces **Developmental:** N/A	
Developmental toxicity *cis* isomer	New Zealand White rabbits (16 females/dose)	**Maternal:** NOAEL: 4 mg/kg bw/day LOAEL: 10 mg/kg bw/day **Maternal:** **≥ 10 mg/kg bw/day:** body weight loss; ↓ bwg ; ↓ fc ↑ late resorptions **Developmental:** NOAEL: undetermined LOAEL: 2 mg/kg bw/day **≥ 2 mg/kg bw/day:** ↑ limb malformations, oligodactyly, brachydactyly	1405644
Developmental toxicity *cis* isomer	New Zealand White rabbits (18 – 20 females/dose)	**Maternal:** NOAEL: 10 mg/kg bw/day LOAEL: 40 mg/kg bw/day **40 mg/kg bw/day:** ↓ bwg GD 7 – 20 and overall; ↓ fc GD 7 – 14 and total treatment ↓ live foetuses & live foetuses/dam ↑ total and late resorptions ↑ postimplantation loss **Developmental:** NOAEL: 2 mg/kg bw/day LOAEL: 10 mg/kg bw/day **≥ 10 mg/kg bw/day:**	145645

Study Type	Species	Results^a (mg/kg/day in M/F)	Reference
		↑ malformations – umbilical hernia, displaced kidneys ↑ variations – connected jugal to maxilla	
Developmental toxicity 1991 *cis:trans* isomers	New Zealand White rabbit (16 – 17/dose – Part I; 18 – 19/dose – Part II)	**Maternal:** NOAEL: 4 mg/kg bw/day LOAEL: 10 mg/kg bw/day **≥ 10 mg/kg bw/day:** ↑ total and late resorptions and total resorptions/dam **Developmental:** NOAEL: 2 mg/kg bw/day LOAEL: 4 mg/kg bw/day **≥ 4 mg/kg bw/day:** ↑ craniofacial malformations; ↑ subcapsular liver cysts	145646
Preliminary Developmental Toxicity	New Zealand White [Hra: (NZW)SPF] rabbits (10/dose)	**Maternal:** **≥ 20 mg/kg bw/day:** ↑ resorptions/dam; ↑ postimplantation loss **Developmental:** **≥ 20 mg/kg bw/day:** ↑ resorptions/dam; ↑ postimplantation loss	145647
Developmental Toxicity 1996 *cis:trans* isomers	New Zealand White [Hra: (NZW)SPF] rabbits (10/dose)	**Maternal:** NOAEL: 5/6.25 mg/kg bw/day LOAEL: 10/8.42 mg/kg bw/day **≥ 10 mg/kg bw/day:** ↑ abs total and early resorptions; ↑ litters with any resorptions; ↑ postimplantation loss **Developmental:** NOAEL: 5/6.25 mg/kg bw/day LOAEL: 10/8.42 mg/kg bw/day **≥ 10 mg/kg bw/day:** ↑ abs total and early resorptions; ↑ litters with any resorptions; ↑ postimplantation loss ↑ dilation of lateral brain ventricles	1405648
Subchronic Neurotoxicity Study – 2 weeks	CD (Crl:CD®(SD) IGS BR) rats (5/sex/dose)	**≥ 100 ppm:** ↓ final bw (5.5%) and bwg (day 0 – 3 11.1%; day 7 – 10 16.7%) (♂)	1405636
Subchronic Neurotoxicity Study – 4 weeks	CD (Crl:CD®(SD) IGS BR) rats (10/sex/dose)	**≥ 170 ppm:** ↓ bw (6.6%), bwg (11.7%) and fc in wk 1 (♀)	1405637

Study Type	Species	Results^a (mg/kg/day in M/F)	Reference
2-week hepatic drug-metabolizing enzyme induction, cell proliferation and reactive oxygen spp production study in mice	ICR (Crj:Cd-1) Mouse (18 females/dose + positive control)	**≥ 300 ppm:** ↓ bw wk 2 (7.1%); ↓ fc wk 2 ↓ chol; ↓ bilirubin (14d) ↑ liver wts @ 3 d ↑ microsomal protein content, ethoxycoumarin O-dealkylase activity, pentoxyreorufin O-dealkylase activity (7d) ↑ cytochrome P-450, CYP2B, CYP3A (7d) ↑ lipid peroxide stress marker (14 d) ↑ hepatocellular hypertrophy; ↑ hepatocellular vacuolation (lipid droplets)	1405624
Gene mutations in mammalian cells in *vitro*	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA1538 31.25 - 5000 µg/plate; with and without activation	Negative	1405653
In *vivo* unscheduled DNA synthesis	Primary rat hepatocytes (male SD rats) 0, 400, 1000 or 2000 mg/kg (single oral dose; primary cultures scored for UDS 4 and 16 hours after dose administration)	Negative	1405656
In *vitro* mammalian chromosomal aberration	Chinese hamster ovary cells 0, 6.25, 25, 50, 100, 200, 400 µg/mL without activation and with activation	positive with activation at low concentrations negative without	1405655
In *vivo* mammalian cytogenetics	Male and female CD-1 (ICR) mice 0, 400, 1000 or 2000 mg/kg (single oral dose; bone marrow harvested 24, 48 and 72 hours post-dosing)	Negative – with reservations about the study conduct	1405654

Study Type	Species	Results[a] (mg/kg/day in M/F)	Reference
Metabolism		**Absorption and Excretion:** The majority of the studies were performed with [Cyclopentyl-^{14}C]WL148271. Elimination was rapid, extensive and predominantly through the faeces in both males and females, though females exhibited more urinary elimination than males. In low dose studies, 93 – 96% was excreted at the end of 3 days and 95% was excreted at the end of 5 days in high dose studies. Females are exposed to more of the test substance than males as indicated by area under the curve, half-life and repetitive accumulation ratios. At 200 mg/kg bw there is a possible saturation of the elimination pathway, though half-life and repetitive accumulation ratios are unaffected by dose. Radioactivity peaked in most organs at 0.5 hours in low dose studies and at 4 hours in high dose studies. In both situations, residual radioactivity was found in the target organs at the end of the observation period. In repeat dose studies, patterns of accumulation were unaffected, though ratios of radioactivity indicated some chance of bioaccumulation. A bile cannulated study on [Cyclopentyl-^{14}C]WL136184 (the *cis* isomer of the TGAI), indicated that the isomer was very extensively absorbed and quickly excreted in males and females. Recovery was over 95% in both sexes, with both sexes excreting the majority in the bile and females excreting more radioactivity in the urine than males. In the bile cannulation study, very little radioactivity was excreted in the faeces. Excretion was slightly faster in females; however, both males and females excreted $\geq$ 50% of the administered dose in the first 6 hours. A study on [Triazole-^{14}C]WL136184, indicated much the same information as the metabolism studies on the mixture of the *cis* and *trans* isomers. The compound was metabolized extensively and excreted quickly. The majority of the excretion occurred in the first four days via the faecal and, less so, the urinary routes. **Distribution:** Target organs are the adrenal glands, liver and GI tract in both sexes, with other reservoirs being the blood, kidney, skin and fat. Females retained 10X the radioactivity in the liver than did males; however, males retained more radioactivity in the adrenal cortex than females. The radioactivity in the GI tract was found in the contents as opposed to the tissues.	

Study Type	Species	Results[a] (mg/kg/day in M/F)	Reference
		Metabolism: Characterization of the metabolites was poor with only 37 and 50% of the metabolites characterized in males and females, respectively. The most common metabolites retained were M1, a monohydroxy metabolite, and M12 faecal and M12 urinary, a carboxy-metabolite. M19, a monohydroxy metabolite, occurred in relatively high percentages in females, but less so in males. The parent compound was found at 2% concentrations in males and females, indicating a possible biliary path for the majority of the faecal metabolites. In the *cis* isomer, less than 1% of the parent compound was discovered during the identification of the metabolites, indicating a high probability of biliary excretion. The two major metabolites were M1 and M12. The proposed metabolic pathway for the *cis* isomer is a monohydroxylation followed by a carboxylation of WL136184.	

a Effects observed in males as well as females unless otherwise reported

Table 4 Toxicology Endpoints for Use in Health Risk Assessment for Metconazole

Exposure Scenario	RfD (mg/kg bw/day)	Study NOAEL (or LOAEL)	CAF or Target MOE[1]
Acute dietary, (♀ 13 – 49)	0.002	NOAEL = 2 mg/kg bw PMRA 1405646 Rabbit Developmental Toxicity Study (craniofacial malformations, liver variations)	1000 PCPA = 10-fold
Chronic Dietary (♀ 13 – 49)	0.002	NOAEL = 2 mg/kg bw/day PMRA 1405646 Rabbit Developmental Toxicity Study (craniofacial malformations, liver variations)	1000 PCPA = 10-fold
Chronic Dietary (gen)	0.0044	NOAEL = 0.44 mg/kg bw/day Combined chronic and oncogenicity (liver and adrenal gland changes)	100 PCPA = 1-fold
q_1^*	Based on skin sarcomas in male mice 1.02×10^{-2}		
Short-term Dermal[2]		NOAEL = 2 mg/kg bw/day PMRA 1405646 Rabbit Developmental Toxicity Study (craniofacial malformations, liver variations)	1000 PCPA = 10-fold
Intermediate-term Dermal		NOAEL = 2 mg/kg bw/day PMRA 1405646 Rabbit Developmental Toxicity Study (craniofacial malformations, liver variations)	1000 PCPA = 10-fold

[1] CAF (Composite assessment factor) refers to the total of uncertainty and PCPA factors for dietary and residential risk assessments; MOE refers to target MOE for occupational assessments

[2] Since an oral NOAEL was selected, a dermal absorption factor is used in a route-to-route extrapolation

Table 5 PHED unit exposure estimates for mixer/loader and applicators while handling Caramba Fungicide (µg/kg bw/day)

Scenario		Dermal	Adjusted dermal [a]	Inhalation	Total [b]
Mixer/loader PHED estimates (Liquid)					
A	Open mixing/loading (cotton coveralls, single layer and gloves)	32.77	6.88	1.60	8.48
B	Closed mixing/loading (cotton coveralls, single layer and gloves)	9.61	2.02	0.11	2.13
Applicator PHED estimates					
C	Groundboom closed cab (cotton coveralls, single layer, no gloves)	4.42	0.93	0.06	0.99
D	Aerial - liquid (single layer, no gloves)	9.66	2.03	0.07	2.10
Mixer/loader and applicator PHED estimates					
A+C	**Farmers and custom applicators (OP):** Open mixing/loading (cotton coveralls, single layer and gloves) and groundboom closed cab (cotton coveralls, single layer, no gloves)	37.19	7.81	1.66	9.47
B + C	**Custom applicators (CML):** Closed mixing/loading (cotton coveralls, single layer, gloves) and groundboom closed cab (cotton coveralls, single layer, no gloves	14.03	2.95	0.17	3.12
A	**Aerial mixer/loader (OP):** Open mixing/loading (cotton coveralls, single layer and gloves)	32.77	6.88	1.60	8.48
C	**Aerial mixer/loader (CML):** Closed mixing/loading (cotton coveralls, single layer and gloves)	9.61	2.02	0.11	2.13
D	**Aerial applicator:** Aerial - liquid (single layer, no gloves)	9.66	2.03	0.07	2.10

OP = open pour, CML = closed mixing/loading systems

[a] The dermal unit exposure was adjusted for 21% dermal absorption.

[b] Total unit exposure = Adjusted dermal unit exposure + Inhalation unit exposure

Table 6 Non-cancer risk assessment for M/L/A scenarios: Cotton coveralls over single layer and chemical-resistant gloves except for aerial applicators (single layer), closed cab for all groundboom applications, closed mixing/loading for custom applicators and aerial mixer/loaders

Scenario	PHED unit exposure (µg/kg a.i. handled)	ATPD [a] (ha/day)	Rate (kg a.i./ha)	Daily exposure [b] (µg/kg bw/day)	MOE [c]
Cereals (wheat, rye, barley, oats)					
GB M/L/A Farmer	9.47	107	0.09	1.30	1535
GB M/L/A Custom (OP)	9.47	360	0.09	4.38	**456**
GB M/L/A Custom (CML)	3.12	360	0.09	1.44	1387
Aerial M/L (OP)	8.48	400	0.09	4.36	**459**
Aerial M/L (CML)	2.13	400	0.09	1.09	1827

Scenario	PHED unit exposure (µg/kg a.i. handled)	ATPD [a] (ha/day)	Rate (kg a.i./ha)	Daily exposure [b] (µg/kg bw/day)	MOE [c]
Aerial A	2.10	400	0.09	1.079	1853
Soybeans and wheat (lower rate)					
GB M/L/A Farmer	9.47	107	0.063	0.91	2193
GB M/L/A Custom (OP)	9.47	360	0.063	3.07	**652**
GB M/L/A Custom (CML)	3.12	360	0.063	1.010	1981
Aerial M/L (OP)	8.48	400	0.063	3.05	**655**
Aerial M/L (CML)	2.13	400	0.063	0.766	2611
Aerial A	2.10	400	0.063	0.755	2647
Sugar beets					
GB M/L/A Farmer	9.47	107	0.1125	1.63	1228
GB M/L/A Custom (OP)	9.47	360	0.1125	5.48	**365**
GB M/L/A Custom (CML)	3.12	360	0.1125	1.80	1109
Aerial M/L (OP)	8.48	400	0.1125	5.45	**367**
Aerial M/L (CML)	2.13	400	0.1125	1.37	1462
Aerial A	2.10	400	0.1125	1.35	1482

GB = groundboom, M/L/A = mixer/loader/applicator, M/L = mixer/loader, A = applicator
OP = open pour, CML = closed mixing/loading systems

[a] Default values of area treated per day (ATPD)

[b] Daily exposure = (PHED unit exposure [µg/kg a.i. handled] × ATPD [ha/day] × Rate [kg a.i./day]) / (70 kg bw)
(Note that the PHED unit exposure is already adjusted for 21% dermal absorption.)

[c] MOE = (NOAEL [mg/kg bw/day] × [1000 µg/mg]) / Daily exposure [µg/kg bw/day]
NOAEL = 2 mg/kg bw/day, target MOE = 1000 based on rabbit developmental study
Calculated MOEs in bold are below the target MOE.

Table 7 Maximum acceptable amount handled and when open mixing/loading

Crop	PHED Unit Exposure (µg/kg a.i. handled) [a]	Amount handled per day (kg a.i./day)	Daily Exposure (mg/kg bw/day) [b]	MOE [c]
Cereals	9.47	14.78	0.00200	1000
Wheat (lower rate) and soybeans				
Sugar beets				

[a] PHED Unit Exposure for M/L/A workers: coveralls over single layer and chemical-resistant gloves, open mixing/loading and closed cab groundboom application

[b] Daily exposure = (PHED unit exposure [µg/kg a.i. handled] × Amount handled per day [kg a.i./day]) / (70 kg bw)
(Note that the PHED unit exposure is already adjusted for 21% dermal absorption.)

[c] MOE = (NOAEL [mg/kg bw/day] × [1000 µg/mg]) / Daily exposure [µg/kg bw/day]
NOAEL = 2 mg/kg bw/day, target MOE = 1000 based on rabbit developmental study

Table 8 **Cancer risk assessment for M/L/A scenarios: Cotton coveralls over single layer and chemical-resistant gloves except for aerial applicators (single layer), closed cab for all groundboom applications, closed mixing/loading for custom applicators and aerial mixer/loaders**

Scenario	PHED unit exposure (µg/kg a.i. handled)	ATPD [a] (ha/day)	Rate (kg a.i./ha)	ADD (mg/kg bw/day) [b]	Days of exposure per year	LADD [c]	Cancer Risk [d]
Cereals (wheat, rye, barley, oats)							
GB M/L/A Farmer	9.47	60	0.09	0.000731	1	1.07×10^{-6}	1.09×10^{-8}
GB M/L/A Custom	3.12	240	0.09	0.000962	3	4.22×10^{-6}	4.30×10^{-8}
Aerial M/L	2.13	318	0.09	0.000870	3	3.81×10^{-6}	3.89×10^{-8}
Aerial A	2.10	318	0.09	0.000858	3	3.76×10^{-6}	3.84×10^{-8}
Winter wheat (lower rate)							
GB M/L/A Farmer	9.47	60	0.063	0.000511	1	7.47×10^{-7}	7.62×10^{-9}
GB M/L/A Custom	3.12	240	0.063	0.000673	146	1.44×10^{-4}	1.46×10^{-6}
Aerial M/L	2.13	318	0.063	0.000609	146	1.30×10^{-4}	1.33×10^{-6}
Aerial A	2.10	318	0.063	0.000601	146	1.28×10^{-4}	1.31×10^{-6}
Spring wheat (lower rate)							
GB M/L/A Farmer	9.47	60	0.063	0.000511	1	7.47×10^{-7}	7.62×10^{-9}
GB M/L/A Custom	3.12	240	0.063	0.000673	83	8.16×10^{-5}	8.33×10^{-7}
Aerial M/L	2.13	318	0.063	0.000609	83	7.39×10^{-5}	7.53×10^{-7}
Aerial A	2.10	318	0.063	0.000601	83	7.28×10^{-5}	7.43×10^{-7}
Soybean							
GB M/L/A Farmer	9.47	60	0.063	0.000511	2	1.49×10^{-6}	1.52×10^{-8}
GB M/L/A Custom	3.12	240	0.063	0.000673	77	7.57×10^{-5}	7.72×10^{-7}
Aerial M/L	2.13	318	0.063	0.000609	77	6.85×10^{-5}	6.99×10^{-7}
Aerial A	2.10	318	0.063	0.000601	77	6.76×10^{-5}	6.89×10^{-7}
Sugar beets							
GB M/L/A Farmer	9.47	60	0.1125	0.000913	2	2.67×10^{-6}	2.72×10^{-8}
GB M/L/A Custom	3.12	240	0.1125	0.00120	76	1.33×10^{-4}	1.36×10^{-6}
Aerial M/L	2.13	318	0.1125	0.001088	76	1.21×10^{-4}	1.23×10^{-6}
Aerial A	2.10	318	0.1125	0.001073	76	1.19×10^{-4}	1.21×10^{-6}

[a] Default values for area treated per day (ATPD)

[b] ADD = Absorbable daily dose
= (PHED unit exposure [µg/kg a.i. handled] × ATPD [ha/day] × Rate [kg a.i. day]) / (70 kg bw × 1000 µg/mg)
(Note that the PHED unit exposure is already adjusted for 21% dermal absorption.)

[c] LADD = Lifetime average daily dose
= [ADD × (# days of exposure/yr) × (40 yrs working duration)] / [(365 days/yr) × (75 yrs life expectancy)]

[d] Cancer risk = LADD (mg/kg bw/day) × q_1* (mg/kg bw/day)$^{-1}$; q_1* = 1.02×10^{-2}

Table 9 Postapplication exposure and risk estimates for re-entry workers scouting and irrigating

Crop(s)	Application rate ($\mu g/cm^2$)	# of applications	Min application interval	Peak DFR [a] ($\mu g/cm^2$)	Transfer coefficient [b] (cm^2/hr)	Exposure [c] (mg/kg bw/day)	MOE [d]	REI
Cereals (including wheat)	0.9	1	-	0.180	1500	0.0032	617	5 days
Soybeans	0.63	2	10 days	0.170	1500	0.0031	654	4 days
Sugar beets	1.125	2	14 days	0.277	1500	0.0050	402	9 days

[a] Peak DFR determined using default of 20% dislodgeable from foliage, 10% dissipation per day

[b] Transfer coefficient values are as documented in USEPA Science Advisory Council for Exposure. Policy Number 003.1. 7 May 1998

[c] Exposure = (Peak DFR [$\mu g/cm^2$] × TC [cm^2/hr] × 4 hr/day × 21% dermal absorption) / (70 kg bw × 1000 [$\mu g/mg$])

[d] Based on NOAEL of 2 mg/kg bw/day, target MOE of 1000 from rabbit developmental study

Table 10 Postapplication cancer risk estimates for re-entry workers scouting and irrigating

Crop(s)	TWA DFR ($\mu g/cm^2$) [a]	Transfer coefficient [b] (cm^2/hr)	ADD [c] (mg/kg bw/day)	# days of exposure per year	LADD [d] (mg/kg bw/day)	Cancer Risk [e]
Cereals	0.0123	1500	0.000222	104	3.37×10^{-5}	3.44×10^{-7}
Winter wheat (lower rate)	0.0034	1500	0.000062	168	1.52×10^{-5}	1.55×10^{-7}
Spring wheat (lower rate)	0.0075	1500	0.000134	120	2.35×10^{-5}	2.40×10^{-7}
Soybean	0.0180	1500	0.000324	100	4.73×10^{-5}	4.83×10^{-7}
Sugar beets	0.0285	1500	0.000513	113	8.46×10^{-5}	8.63×10^{-7}

[a] TWA DFR = time-weighted average DFR = average of DFR values from the first application to the end of scouting

[b] Transfer coefficient values are as documented in USEPA Science Advisory Council for Exposure. Policy Number 003.1. 7 May 1998

[c] ADD = Absorbable daily dose
= (TWA DFR [$\mu g/cm^2$] × TC [cm^2/hr] × 4 hr/day × 21% dermal absorption) / (70 kg bw × 1000 μg/mg)

[d] LADD = Lifetime average daily dose
= [ADD × (# days of exposure/yr) × (40 yrs working duration)] / [(365 days/yr) × (75 yrs life expectancy)]

[e] Cancer risk = LADD (mg/kg bw/day) × q_1* $(mg/kg\ bw/day)^{-1}$; q_1* = 1.02E-2

Table 11 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN BANANA	**PMRA 1405681**
Radiolabel Position	[chlorophenyl-U-^{14}C]metconazole (specific activity 10.9 µCi/mg) and [triazole-3,5-^{14}C]metconazole (specific activity 9.47 µCi/mg)
Test Site	Greenhouse
Treatment	Foliar
Rate	Five applications at 0.139-0.1413 kg a.i./ha/application for a total of 0.695-0.715 kg a.i./ha/season
End-use product	Radiolabeled test substances were dissolved in n-amyl alcohol and formulated in mineral spirits:surfactant (Shellsol:Dobanol, 2:1, v:v). The guarantee of metconazole was *ca.* 0.11 g a.i./L for both labels.
Preharvest interval	0 days

Radiolabel Position		**[chlorophenyl-U-^{14}C]**	**[triazole-3,5-^{14}C]**
Matrix	**PHI (days)**	**TRR (ppm)**	**TRR (ppm)**
Whole fruit	0	0.93	1.37
Peel	0	2.54	1.62
Pulp	0	0.78	0.61

Metabolites Identified	**Major Metabolites (> 10% TRR and >0.010 ppm)**		**Minor Metabolites (< 10% TRR and >0.010 ppm)**	
Radiolabel Position	[chlorophenyl-U-^{14}C]	[triazole-3,5-^{14}C]	[chlorophenyl-U-^{14}C]	[triazole-3,5-^{14}C]
Whole fruit	metconazole	metconazole	M1, MHM, M11	TA, M1, MHM, M11
Peel	metconazole	metconazole	M1, MHM, M11	TA, M1, MHM, M11
Pulp	metconazole	metconazole	M1, MHM, M11	TA, M1, M11

NATURE OF THE RESIDUE IN CANOLA	**PMRA 1405682 and 1405680**
Radiolabel Position	[chlorophenyl-U-^{14}C]metconazole (specific activity 10 µCi/mg) and [triazole-3,5-^{14}C]metconazole (specific activity 9.58 µCi/mg)
Test Site	Outdoor plots
Treatment	Foliar
Rate	Two broadcast foliar at 0.263-0.264 kg a.i./ha/application for total application rates of 0.527-0.529 g a.i./ha.
End-use product	Radiolabeled test substances were dissolved in n-amyl alcohol and formulated in mineral spirits:surfactant (Shellsol:Dobanol, 2:1, v:v). The guarantee of metconazole was *ca.* 0.63 g a.i./L for both labels.
Preharvest interval	Samples of canola foliage were harvested immediately following the first and second applications (0 days after treatment one (0-DAT1) and 0-DAT2, respectively), and 14 and 28 days after the second application (14- and 28-DAT2). Samples of canola pod (pod shell and foliage combined) and seed were harvested at maturity, 28-DAT2, and allowed to dry in the field for 16-22 days.

Radiolabel Position		**[chlorophenyl-U-^{14}C]**	**[triazole-3,5-^{14}C]**
Matrix	**PHI (days)**	**TRR (ppm)**	**TRR (ppm)**
0-DAT1 Foliage	0	10.79	8.76
Foliage	0	14.95	9.89
Foliage	14	5.60	8.63
Foliage	28	5.92	20.35
Pod	28	20.67	19.62
Seed	28	1.85	2.39

Metabolites Identified	Major Metabolites (> 10% TRR and >0.010 ppm)		Minor Metabolites (< 10% TRR and >0.010 ppm)	
Radiolabel Position	[chlorophenyl-U-^{14}C]	[triazole-3,5-^{14}C]	[chlorophenyl-U-^{14}C]	[triazole-3,5-^{14}C]
Foliage PHI 0	metconazole	metconazole	M11	—
Foliage PHI 14	metconazole	metconazole	M11	M11, TA
Foliage PHI 28	metconazole	metconazole	M11	M11, TA
Canola pod	metconazole	metconazole	M11	M11, TA
Canola seed	metconazole	TA, metconazole	M11	M11

NATURE OF THE RESIDUE IN MANDARIN	PMRA 1405678
Radiolabel Position	[cyclopentyl-^{14}C]metconazole (specific activity 343307.4 dpm/µg) and [triazole-3,5-^{14}C]metconazole (specific activity 388331.3 dpm/µg)
Test Site	Greenhouse
Treatment	Foliar
Rate	A single broadcast foliar application at 0.200 kg a.i./ha.
End-use product	Radiolabeled test substances were dissolved in methanol and formulated with aqueous NF-151 solution. The guarantee of metconazole was *ca.* 0.05 g a.i./L for both labels.
Preharvest interval	0, 28 and 56 day

Radiolabel Position		[cyclopentyl-^{14}C]	[triazole-3,5-^{14}C]
Matrix	**PHI (days)**	**TRR (ppm)**	**TRR (ppm)**
Leaves	0	4.22	4.84
	28	3.50	3.66
	56	3.09	3.31
Fruit	0	0.10	0.13
	28	0.10	0.10
	56	0.11	0.07

Metabolites Identified	Major Metabolites (> 10% TRR and >0.010 ppm)		Minor Metabolites (< 10% TRR and >0.010 ppm)	
Radiolabel Position	[cyclopentyl-^{14}C]	[triazole-3,5-^{14}C]	[cyclopentyl-^{14}C]	[triazole-3,5-^{14}C]
Leaves PHI 0	metconazole	metconazole	M21, MHM aglycone, DHM aglycone, M2 aglycone, M1 aglycone. Note: M21 was detected at all PHIs in leaves and fruit. All other minor metabolites were detected only at a PHI of 56 days	
Leaves PHI 28	metconazole	metconazole		
Leaves PHI 56	metconazole	metconazole		
Fruit PHI 0	metconazole	metconazole		
Fruit PHI 28	metconazole	metconazole		
Fruit PHI 56	metconazole	metconazole		

NATURE OF THE RESIDUE IN PEA	PMRA 1405679
Radiolabel Position	[chlorophenyl-U-^{14}C]metconazole (specific activity 9.99 µCi/mg) and [triazole-3,5-^{14}C]metconazole (specific activity 10 µCi/mg)
Test Site	Pots – outdoor (field)
Treatment	Foliar
Rate	The total application rates for the chlorophenyl and triazole labels were ca. 0.211 kg a.i./ha following one application, 0.416-0.418 kg a.i./ha following two applications and 0.623-0.626 kg a.i./ha following three applications.
End-use product	Radiolabeled test substances were formulated as a soluble concentrate which was diluted with water to give a final spray solution with a nominal concentration of 0.360 g/L metconazole.
Preharvest interval	Samples of immature pea foliage were harvested immediately following each application [0 days after treatment 1 (0-DAT1), 0-DAT2 and 0-DAT3], and samples of pea seed and straw were collected 13-DAT2 (green pea) and 15-DAT3 (dry pea).

Radiolabel Position		[chlorophenyl-U-^{14}C]	[triazole-3,5-^{14}C]
Matrix	**PHI (days)**	**TRR (ppm)**	**TRR (ppm)**
0-DAT1 Foliage	0	5.13	9.58
0-DAT2 Foliage	13	12.85	5.38
0-DAT3 Foliage	13	21.28	20.76
13-DAT2 Straw	13	9.94	10.20
15-DAT3 Straw	15	168.2	63.38
13-DAT2 Seed	13	0.038	1.62
15-DAT3 Seed	15	0.226	3.92

Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	[chlorophenyl-U-^{14}C]	[triazole-3,5-^{14}C]	[chlorophenyl-U-^{14}C]	[triazole-3,5-^{14}C]
Foliage PHI 0	Metconazole	Metconazole	—	—
Straw PHI 15	Metconazole	Metconazole	—	—
Seed (green) PHI 13	Metconazole	TA	—	Metconazole
Seed (dry) PHI 15	Metconazole	TA	—	Metconazole

NATURE OF THE RESIDUE IN WHEAT	**PMRA 1405676 and 1405677**
Radiolabel Position	[cyclopentyl- ^{14}C]metconazole (specific activity 17.5 µCi/mg) and [triazole-3,5-^{14}C]metconazole (specific activity 23.2 µCi/mg)
Test Site	Outdoor
Treatment	Foliar
Rate	A single foliar broadcast application was made to wheat at 0.360 kg a.i./ha (cyclopentyl) or 0.370 kg a.i./ha (triazole) at Zadoks growth stage 57-60.
End-use product	Radiolabeled test substances were formulated as emulsifiable concentrates to a guarantee of *ca.* 1 g a.i./L.
Preharvest interval	Samples of wheat grain and straw were harvested at PHIs of 61-73 days.

Radiolabel Position		**[cyclopentyl-^{14}C]**	**[triazole-3,5-^{14}C]**
Matrix	**PHI (days)**	**TRR (ppm)**	**TRR (ppm)**
Wheat grain	61-73	0.074	0.66
Wheat straw	61-73	5.88	6.33

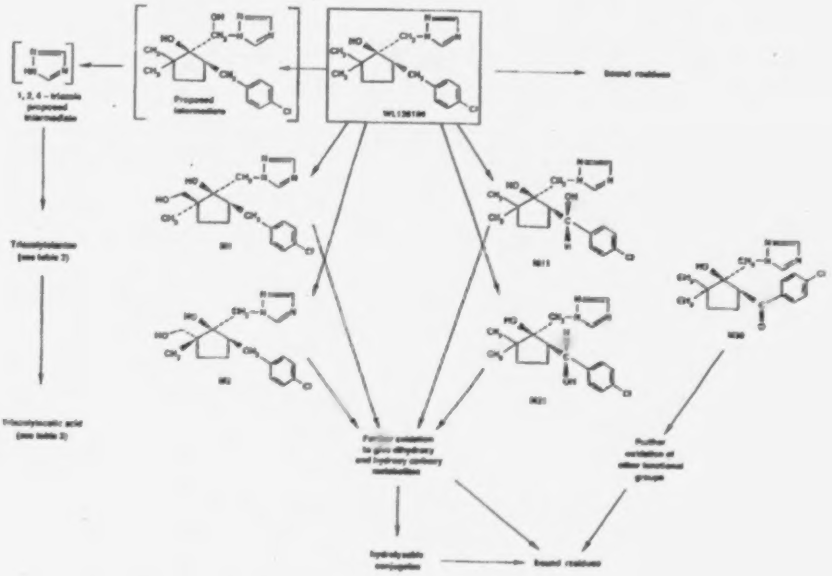
Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	[cyclopentyl-^{14}C]	[triazole-3,5-^{14}C]	[cyclopentyl-^{14}C]	[triazole-3,5-^{14}C]
Wheat grain	—	TA, TAA	—	—
Wheat straw	metconazole	metconazole	M1, M11, M2, M30	M2, M11, M30, TAA

CONFINED ACCUMULATION IN ROTATIONAL CROPS – RADISH, LETTUCE AND WHEAT	**PMRA 1403182**
Radiolabel Position	[cyclopentyl-^{14}C]-metconazole (17.0 µCi/mg) or [triazole-3,5-^{14}C]-metconazole (20.4 µCi/mg)
Test site	Soil was placed into pots and crops were grown in either a temperature controlled glasshouse or in controlled environmental chambers.
Formulation used for trial	Radiolabeled test substances were formulated as emulsifiable concentrates to a guarantee of *ca.* 106 g a.i./L.
Application rate and timing	Soil was treated with approximately 400 g a.i./ha, aged for 30 or 120 days and then sown with radish, lettuce or wheat. The harvest of the mature radish, lettuce and wheat took place approximately 69, 77 and 189 days after sowing, respectively.

Metabolites Identified		**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Matrix	**PBI (days)**	[cyclopentyl- ^{14}C]	[triazole-3,5-^{14}C]	[cyclopentyl- ^{14}C]	[triazole-3,5-^{14}C]
Lettuce	30	Not examined	metconazole, TA	Not examined	None identified
	120	metconazole	Triazole conjugates	None identified	metconazole
Radish foliage	30	metconazole	metconazole	M30	M30
	120	Not examined	None identified	Not examined	metconazole, M30
Radish root	30	metconazole	metconazole, TA	M30	M30
	120	Not examined	metconazole, TA	Not examined	M30
Wheat grain	30	Not examined	TA	Not examined	None identified
	120	Not examined	TA, TAA	Not examined	None identified
Wheat straw	30	Not examined	metconazole	Not examined	M30
	120	None identified	None identified	metconazole, M30	metconazole, M30

Metabolism of metconazole was similar in all primary and rotated crops examined. The major metabolic pathway involved oxidative hydroxylation of the methylene groups, the methyl groups on the cyclopentyl ring and possibly of the cyclopentyl ring. In addition, monohydroxylation may occur at the various pro-chiral carbons of metconazole. Further oxidation of the hydroxylated metabolites to form dihydroxylated or carboxylated derivatives occurred in the mandarin study. Aglycones of monohydroxylated and dihydroxylated metabolites were observed in all crops. TA and triazole conjugates were identified in canola, pea and wheat indicating that the methylene between the triazole and cyclopentyl rings is susceptible to oxidative hydroxylation

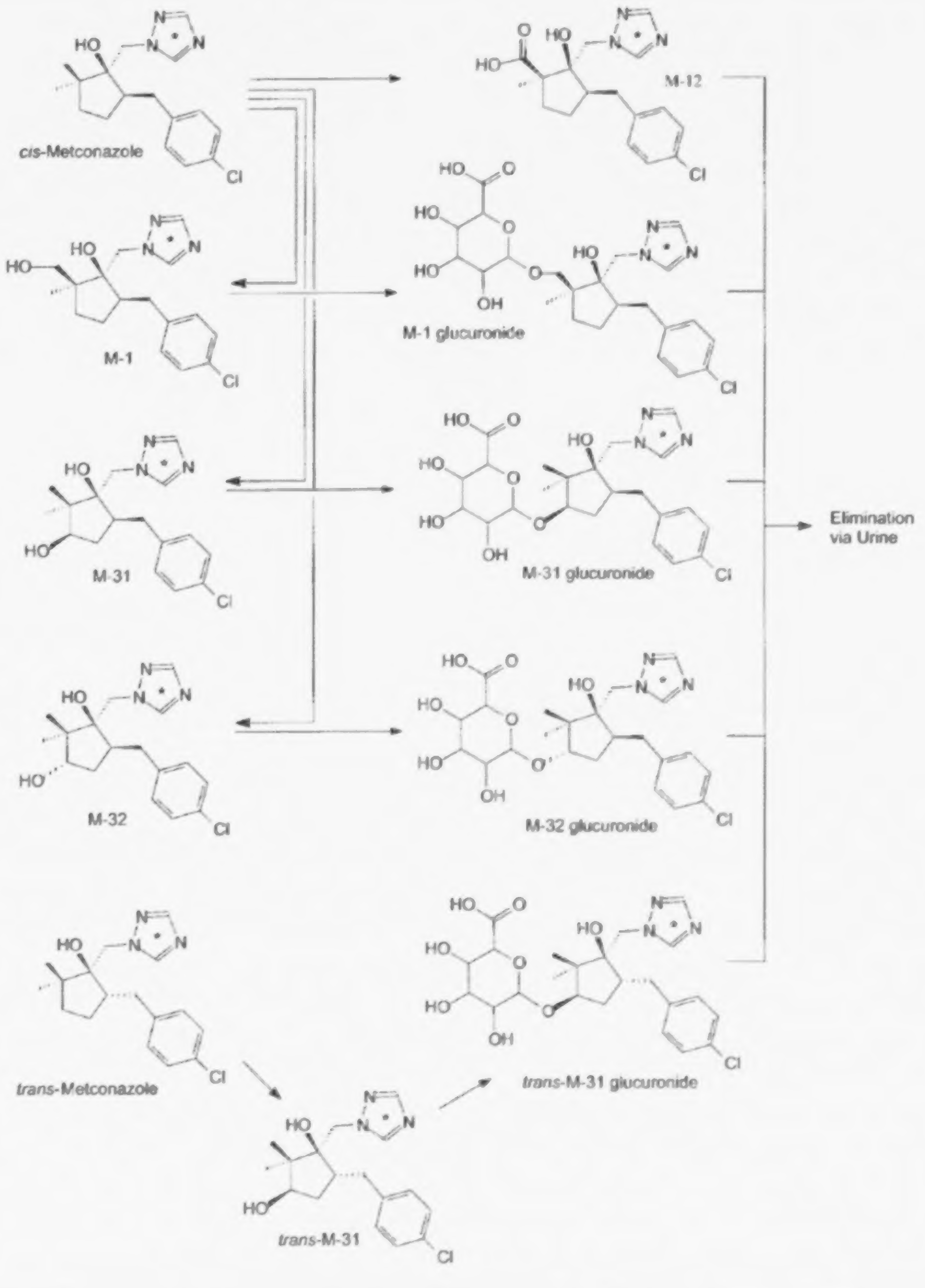
Proposed metabolic scheme in Wheat


1, 2, 4 - triazole proposed intermediate
Proposed intermediate
bound residues
Triazolylalanine (see table 3)
Triazolylacetic acid (see table 3)
M1
M2
M11
M21
M30
Further oxidation to give dihydroxy and hydroxy carboxy metabolites
Further oxidation of other functional groups
hydrolysable conjugates
bound residues

NATURE OF THE RESIDUE IN LAYING HEN			**PMRA 1405673**	
Two groups of five hens were orally dosed for 4.5 consecutive days with [cyclopentyl-^{14}C]-metconazole (specific activity 0.909 GBq/mmole) and [triazole-^{14}C]-metconazole (specific activity 0.907 GBq/mmole) at 14 and 12.6 mg/kg bw/day, respectively. Hens were sacrificed 4.5 hours following the last dosing and tissue samples of muscle, liver, skin with fat and abdominal fat were collected. The majority of the administered dose was excreted from the treated hens, nevertheless, measurable residues were detected hen tissues and eggs.				
Matrices			**Distribution of Radioactivity (ppm)**	
			[cyclopentyl-^{14}C]	**[triazole-3,5-^{14}C]**
Excreta			14.685	14.463
Muscle, breast			0.031	0.145
Muscle, thigh			0.049	0.152
Fat, abdominal			0.091	0.141
Skin with fat			0.075	0.137
Liver			0.790	0.972
Egg whites			0.047	0.186
Egg yolks			0.088	0.156
Metabolites identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	[cyclopentyl-^{14}C]	[triazole-3,5-^{14}C]	[cyclopentyl-^{14}C]	[triazole-3,5-^{14}C]
Muscle, breast	M1 (+M31), MHM sulfate, M32 sulfate	1,2,4-T	DHM sulfate, CM2, MHM, metconazole	Metconazole, M1 (+ M31), CM2, MHM, DHM sulfate, M32 sulfate, MHM sulfate
Muscle, thigh	M1 (+M31), DHM sulfate, MHM sulfate, CM2	1,2,4-T	metconazole, M32 sulfate, MHM	Metconazole, M1 (+ M31), CM2, MHM, DHM sulfate, M32 sulfate, MHM sulfate
Fat, abdominal	metconazole, M1 (+M31)	metconazole, 1,2,4-T, M1 (+M31)	CM2, MHM, M32 sulfate, MHM sulfate	CM2, MHM, DHM sulfate, M32 sulfate, MHM sulfate
Skin with fat	metconazole, M1 (+M31)	1,2,4-T, metconazole, M1 (+M31)	CM2, MHM sulfate, MHM, DHM sulfate, M32 sulfate	CM2, MHM, M32 sulfate, MHM sulfate
Liver	M1 (+M31), M12 (+ CM2/3), MHM	1,2,4-T	metconazole, M31, M32 (+ CM-1), DCM, CHM, DHM	Metconazole, M1, M31, M12(+CM-2/3), M32 (+CM1), DCM, CHM, DHM MHM, OCM
Egg whites	M1 (+M31), CM2, M32 sulfate, MHM sulfate	1,2,4-T	Metconazole, MHM	metconazole, M1 (+M31), CM2, MHM, M32 sulfate, MHM sulfate
Egg yolks	M1 (+M31), MHM sulfate, metconazole	1,2,4-T	MHM, M32 sulfate, CM2, DMH sulfate	Metconazole, M1 + M31, CM2, MHM, DMH sulfate, M32 sulfate, MHM sulfate

<table>
<tr><th colspan="3">NATURE OF THE RESIDUE IN LACTATING GOAT</th><th colspan="2">PMRA 1405669 and 1405672</th></tr>
<tr><td colspan="5">One (triazole) or two (cyclopentyl) lactating goats were orally dosed for 3-4 days with [cyclopentyl-^{14}C]-metconazole (specific activity 10.33 µCi/mg) or [triazole-^{14}C]-metconazole (specific activity 2.07 GBq/mmole) at levels from 10 to 25 mg/kg bw/day. Milk was collected twice daily and selected samples were separated into cream, curds and whey. Goats were sacrificed 17 to 18 hours following the last dosing and tissue samples of muscle, fat, liver and kidney were collected. The majority of the administered dose was excreted from treated goats, nevertheless, measurable residues were detected goat tissues and milk.</td></tr>
<tr><td colspan="3" rowspan="2">Matrices</td><td colspan="2">Distribution of Radioactivity (ppm)</td></tr>
<tr><td>[cyclopentyl- ^{14}C]</td><td>[triazole-3,5-^{14}C]</td></tr>
<tr><td colspan="3">Urine and faeces</td><td>54.56-68.57 %AD</td><td>28.36 %AD</td></tr>
<tr><td colspan="3">Muscle, fore leg</td><td>0.001-0.005 ppm</td><td>0.004 ppm</td></tr>
<tr><td colspan="3">Muscle, hind leg</td><td>0.004-0.005 ppm</td><td>—</td></tr>
<tr><td colspan="3">Fat</td><td>0.015-0.003 ppm</td><td>0.003 ppm</td></tr>
<tr><td colspan="3">Bile</td><td>3.781-8.514 ppm</td><td>4.260 ppm</td></tr>
<tr><td colspan="3">Bladder urine</td><td>11.206-57.550 ppm</td><td>—</td></tr>
<tr><td colspan="3">Kidney</td><td>0.145-0.276 ppm</td><td>0.117 ppm</td></tr>
<tr><td colspan="3">Liver</td><td>0.456-0.559 ppm</td><td>0.241 ppm</td></tr>
<tr><td colspan="3">Milk</td><td>0.002-0.004 ppm</td><td>0.005 ppm</td></tr>
<tr><td>Metabolites identified</td><td colspan="2">Major Metabolites (> 10% TRR)</td><td colspan="2">Minor Metabolites (< 10% TRR)</td></tr>
<tr><td>Radiolabel Position</td><td>[cyclopentyl- ^{14}C]</td><td>[triazole-3,5-^{14}C]</td><td>[cyclopentyl-^{14}C]</td><td>[triazole-3,5-^{14}C]</td></tr>
<tr><td>Urine</td><td>M12, M1</td><td>Not examined</td><td>M2/M15,
metconazole</td><td>Not examined</td></tr>
<tr><td>Muscle</td><td>metconazole</td><td>Not examined</td><td>None identified</td><td>Not examined</td></tr>
<tr><td>Fat</td><td>metconazole</td><td>Not examined</td><td>None identified</td><td>Not examined</td></tr>
<tr><td>Kidney</td><td>M12, M1</td><td>M31 aglycone,
M12, M1 aglycone</td><td>M2/M15,
metconazole</td><td>M32 aglycone,
metconazole</td></tr>
<tr><td>Liver</td><td>metconazole</td><td>metconazole, M31 aglycone</td><td>None identified</td><td>M12, M1, M31, <i>trans</i>-M31, M32, M1 aglycone, <i>trans</i>-M31 aglycone, M32 aglycone, <i>trans</i>-M31 aglycone</td></tr>
</table>

Proposed Metabolic Scheme in Livestock (Goat)



STORAGE STABILITY IN PLANTS — **PMRA 1590333, 1403166, 1403167, 1403168, 1403169, 1408096 and 1403170**

Residues of metconazole (*cis*- and *trans*-isomers) were stable when stored frozen for 26 months in wheat hay, radish roots and soybean seed; 12 months in carrot, lettuce, rapeseed, rapeseed oil, rye forage, wheat grain and wheat straw; 6 months in banana.

Residues of M11, M21 and M30 were stable when stored frozen for 26 months in wheat grain, hay and straw as well as in sugar beet roots, radish tops and soybean seed.

Residues of triazole were stable when stored frozen for 26 months in radish tops and soybean seed, and 12 months in radish roots and wheat grain. Residues of triazolylacetic acid and triazolylalanine were stable when stored frozen for 26 months in wheat grain, radish roots, radish tops and soybean seed.

Banana Crop Field Trials — **PMRA 1408097-1408108**

GAP: 0.800 kg a.i./ha/season, PHI of 0 days.

Twelve banana field trials were conducted in major banana producing regions including 3 trials in Mexico, 3 trials in Ecuador, 3 trials in Costa Rica and 3 trials in Honduras. At each site CL 900768 200EC containing the active ingredient, metconazole, was applied seven times by aerial broadcast at rates of 131-211 g a.i./ha corresponding to maximum total rates of 0.105-0.114 kg a.i./ha (*ca.* 1.4-fold GAP). Samples of bagged and unbagged bananas were collected after the seventh application had dried (PHI of 0.1 days). Samples were analyzed for *cis*- and *trans*-metconazole according to method M 2722. Residues of *cis*-metconazole and *trans*-metconazole from the treated plots were <0.05 ppm in all whole bananas and banana pulp samples (bagged and unbagged) harvested at a PHI of 0.1 days.

Commodity	Total Application Rate (kg a.i./ha)	PHI (days)	Analyte	Residue Levels (ppm)						
				n	Min.	Max.	HAFT[a]	Median[b]	Mean[b]	Standard Deviation
Banana Pulp (bagged and unbagged)	0.105-0.114	0.1	*cis*-Metconazole	48	<0.05	<0.05	<0.05	<0.05	<0.05	—
			trans-Metconazole		<0.05	<0.05	<0.05	<0.05	<0.05	—
Whole Banana (bagged and unbagged)		0.1	*cis*-Metconazole	48	<0.05	<0.05	<0.05	<0.05	<0.05	—
			trans-Metconazole		<0.05	<0.05	<0.05	<0.05	<0.05	—

Barley Crop Field Trials — **PMRA 1403180**

GAP: 0.090 kg a.i./ha/season, PHI of 30 days.

Twelve barley field trials were conducted in NAFTA Zones 1, 5, 7, 9, 10, 11 and 14 during the 2004-2005 growing season. Plots received two postemergent broadcast foliar applications of metconazole (formulation, BAS 555 01F, 90 g a.i./L SL) at 0.11-0.12 kg a.i./ha/application, with 6-8 day retreatment intervals, for maximum seasonal rates of 0.22-0.24 kg a.i./ha/season (*ca.* 2.7-fold GAP). Barley hay was harvested 7-8 days after the last application and allowed to dry in the field for 0 to14 days prior to collection. Barley grain and straw were harvested 20-21 days after the last application. Additional hay samples were collected 0, 7 and 14 days after the last application, and grain and straw samples were harvested 14, 21, 28 and 35 days after the last application to generate residue decline data. Residues of *cis*- and *trans*-metconazole, M11, M21, M30 and the triazole metabolites (grain only), 1,2,4-T, TA and TAA were quantified using the validated LC/MS/MS method D0508. Residues of *cis*- and *trans*-metconazole generally declined in barley hay, grain and straw with increasing preharvest intervals.

Commodity	Total Application Rate (kg a.i./ha)	PHI (days)	Analyte	Residue Levels (ppm)						
				n	Min.	Max.	HAFT[a]	Median[b]	Mean[b]	Standard Deviation
Grain	0.22-0.23	20-21	*cis*-Metconazole	24	0.09	1.33	1.11	0.40	0.44	0.34
			trans-Metconazole		0.02	0.27	0.23	0.07	0.08	0.06
			cis + *trans* (sum)[c]		0.11	1.60	1.34	0.48	0.52	0.40
			M11		<0.01	0.33	0.31	0.03	0.06	0.08
			M21		<0.01	0.08	0.07	0.01	0.02	0.02
			M30		<0.01	0.05	0.05	0.01	0.02	0.01
			Total Metconazole[d]		0.15	1.83	1.61	0.59	0.62	0.45
Hay	0.22-0.24	7-8	*cis*-Metconazole	24	0.64	3.69	3.69	2.57	2.28	0.99
			trans-Metconazole		0.09	0.74	0.68	0.48	0.42	0.20
			cis + *trans* (sum)[c]		0.73	4.43	4.37	3.03	2.70	1.19
			M11		<0.01	0.38	0.35	0.05	0.08	0.09
			M21		<0.01	0.20	0.19	0.04	0.06	0.05
			M30		<0.01	0.07	0.06	0.01	0.02	0.02
			Total Metconazole[d]		0.80	5.10	5.00	3.15	2.86	1.31
Straw	0.22-0.23	20-21	*cis*-Metconazole	24	0.54	3.94	3.82	2.57	2.35	1.06
			trans-Metconazole		0.09	0.82	0.82	0.50	0.46	0.23
			cis + *trans* (sum)[c]		0.64	4.65	4.56	3.07	2.80	1.29
			M11		0.03	1.08	1.01	0.42	0.39	0.32
			M21		0.04	0.46	0.43	0.11	0.17	0.14
			M30		0.01	0.15	0.15	0.05	0.05	0.04
			Total Metconazole[d]		0.80	5.80	5.65	3.65	3.41	1.45

Oat Crop Field Trials | **PMRA 1403177**

GAP: 0.090 kg a.i./ha/season, PHI of 30 days.

Twelve field trials were conducted in NAFTA Zones 1, 2, 5, 6, 7 and 14 during the 2004-2005 growing season. Plots received two broadcast applications of metconazole (formulation, BAS 555 01F, 90 g a.i./L SL) at 0.11-0.12 kg a.i./ha/application, with 6-8 day retreatment intervals, resulting in total rates of 0.22-0.23 kg a.i./ha/season (*ca.* 2.6-fold GAP). Oat hay samples were harvested at PHIs of 6-8 days and grain and straw samples were harvested at PHIs of 20-21 days, except for one trial where the grain and straw were collected at a PHI of 26 days due to adverse weather conditions that prevented harvest. At one site hay samples were harvested at PHIs of 0, 7 and 14 days and grain and straw samples were harvested at PHIs of 14, 21, 28 and 36 days to examine residue decline. Residues of *cis*- and *trans*-metconazole, M11, M21 and M30 and the triazole metabolites (grain only), 1,2,4-T, TA and TAA were quantified using the validated LC/MS/MS method D0508. Residues of *cis*- and *trans*-metconazole generally declined in oat hay, grain and straw with increasing preharvest intervals.

Commodity	Total Application Rate (kg a.i./ha)	PHI (days)	Analyte	Residue Levels (ppm)						
				n	Min.	Max.	HAFT[a]	Median[b]	Mean[b]	Standard Deviation
Hay	0.22-0.23	6-8	*cis*-Metconazole	24	1.86	10.01	9.58	4.32	5.07	2.36
			trans-Metconazole		0.39	1.66	1.66	0.95	0.96	0.41
			cis + *trans* (sum)[c]		2.29	11.67	11.24	5.25	6.03	2.76
			M11		0.01	0.43	0.08	0.05	0.10	0.13
			M21		0.03	0.12	0.12	0.10	0.08	0.03
			M30		0.01	0.05	0.02	0.02	0.02	0.01
			Total Metconazole[d]		2.57	11.90	11.47	5.68	6.24	2.78
Straw	0.22-0.23	20-26	*cis*-Metconazole	24	0.83	5.07	4.82	1.51	1.83	1.06
			trans-Metconazole		0.15	0.87	0.83	0.30	0.36	0.21
			cis + *trans* (sum)[c]		0.99	5.94	5.65	1.74	2.19	1.26
			M11		0.02	2.48	2.32	0.35	0.44	0.61
			M21		0.02	0.49	0.47	0.06	0.11	0.13
			M30		0.01	0.18	0.17	0.04	0.04	0.04
			Total Metconazole[d]		1.18	9.09	8.61	2.31	2.78	1.95
Grain	0.22-0.23	20-26	*cis*-Metconazole	24	0.04	0.57	0.48	0.23	0.26	0.15
			trans-Metconazole		0.02	0.22	0.08	0.05	0.06	0.04
			cis + *trans* (sum)[c]		0.13	0.68	0.56	0.27	0.32	0.15
			M11		0.01	0.34	0.27	0.09	0.11	0.09
			M21		0.02	0.06	0.06	0.03	0.03	0.02
			M30		0.01	0.06	0.05	0.01	0.02	0.02
			Total Metconazole[d]		0.17	1.14	0.93	0.46	0.48	0.26

Rye Crop Field Trials | **PMRA 1403178**

GAP: 0.090 kg a.i./ha/season, PHI of 30 days.

Five field trials were conducted in NAFTA Zones 2, 5, 7 and 14 during the 2004-2005 growing season. Plots received two broadcast applications of metconazole (formulation, BAS 555 01F; 90 g a.i./L SL) at 0.11 kg a.i./ha/application, with 6-8 day retreatment intervals, resulting in maximum seasonal rates of 0.22-0.23 kg a.i./ha/season (*ca.* 2.6-fold GAP). Rye grain and straw samples were harvested at PHIs of 20-22 days At one site grain and straw samples were harvested at PHIs of 14, 21, 28 and 34 days to examine residue decline. Residues of *cis-* and *trans*-metconazole, M11, M21, M30 and the triazole metabolites (grain only), 1,2,4-T, TA and TAA were quantified using the validated LC/MS/MS method D0508. Residues of *cis-* and *trans*-metconazole were generally stable in rye grain and straw with increasing preharvest intervals.

Commodity	Total Application Rate (kg a.i./ha)	PHI (days)	Analyte	Residue Levels (ppm)						
				n	Min.	Max.	HAFT[a]	Median[b]	Mean[b]	Standard Deviation
Straw	0.22-0.23	20-22	*cis*-Metconazole	10	1.80	7.36	7.16	3.19	3.62	2.00
			trans-Metconazole		0.13	1.43	1.32	0.71	0.64	0.48
			cis + *trans* (sum)[c]		1.93	8.78	8.47	3.90	4.26	2.45
			M11		0.05	0.91	0.76	0.38	0.41	0.31
			M21		0.04	0.14	0.13	0.06	0.08	0.04
			M30		0.01	0.06	0.05	0.04	0.03	0.02
			Total Metconazole[d]		2.02	9.63	9.07	4.42	4.78	2.59
Grain	0.22-0.23	20-22	*cis*-Metconazole	10	0.03	0.13	0.13	0.06	0.07	0.03
			trans-Metconazole		0.01	0.03	0.03	0.01	0.02	0.01
			cis + *trans* (sum)[c]		0.04	0.16	0.15	0.08	0.09	0.04
			M11		<0.01	0.04	0.04	0.03	0.03	0.01
			M21		<0.01	0.01	0.01	0.01	0.01	0.00
			M30		<0.01	0.01	0.01	0.01	0.01	0.00
			Total Metconazole[d]		0.07	0.22	0.21	0.13	0.13	0.05

Wheat Crop Field Trials | **PMRA 1403176**

GAP: 0.090 kg a.i./ha/season, PHI of 30 days.

Fifteen field trials (eight winter wheat and seven spring wheat) were conducted in NAFTA Zones 2, 4, 5, 6, 7, 8, 11 and 14 during the 2004-2005 growing season. Plots received two broadcast foliar applications of metconazole (formulation, BAS 555 01F, 90 g a.i./L SL) at 0.09-0.11 kg a.i./ha/application, with 6-8-day retreatment intervals, for total seasonal rates of 0.20-0.23 kg a.i./ha/season (*ca.* 2.6-fold GAP). Wheat hay was harvested 6-8 days after the last application and allowed to dry in the field or under cover for 0-14 days prior to collection. Wheat grain and straw were harvested 20-22 days after the last application. Additional hay samples were collected from two trials 0, 7-8 and 14 days after the last application, and grain and straw samples were harvested 14, 21-22, 28 and 35-36 days after the last application to generate residue decline data. Residues of *cis*- and *trans*-metconazole, M11, M21, M30 and the triazole metabolites (grain only), 1,2,4-T, TA and TAA were quantified using the validated LC/MS/MS method D0508. Residues of *cis*- and *trans*-metconazole generally declined or remained the same in wheat hay, grain and straw with increasing preharvest intervals.

Commodity	Total Application Rate (kg a.i./ha)	PHI (days)	Analyte	Residue Levels (ppm)						
				n	Min.	Max.	HAFT[a]	Median[b]	Mean[b]	Standard Deviation
Hay	0.22-0.23	6-8	*cis*-Metconazole	30	1.16	11.00	10.90	5.36	5.55	2.51
			trans-Metconazole		0.17	1.72	1.68	0.93	0.95	0.41
			cis + *trans* (sum)[c]		1.33	12.66	12.58	6.24	6.50	2.91
			M11		<0.01	0.48	0.37	0.06	0.10	0.11
			M21		0.03	0.19	0.18	0.08	0.09	0.04
			M30		<0.01	0.06	0.05	0.02	0.02	0.01
			Total Metconazole[d]		1.60	12.80	12.70	6.55	6.71	2.92
Straw	0.20-0.23	20-22	*cis*-Metconazole	30	0.15	8.39	8.29	1.34	2.39	2.48
			trans-Metconazole		0.05	4.72	4.13	0.91	1.23	1.14
			cis + *trans* (sum)[c]		0.27	9.84	9.73	2.75	3.62	2.57
			M11		0.03	1.29	1.08	0.28	0.38	0.35
			M21		0.04	0.45	0.45	0.11	0.15	0.11
			M30		0.01	0.14	0.13	0.04	0.06	0.04
			Total Metconazole[d]		0.40	11.30	11.20	3.65	4.21	2.85
Grain	0.20-0.23	20-22	*cis*-Metconazole	30	0.01	0.10	0.08	0.03	0.03	0.02
			trans-Metconazole		<0.01	0.02	0.02	0.01	0.01	0.00
			cis + *trans* (sum)[c]		0.01	0.12	0.10	0.03	0.04	0.03
			M11		<0.01	0.03	0.03	0.01	0.01	0.01
			M21		<0.01	0.01	0.01	0.01	0.01	0.00
			M30		<0.01	0.01	0.01	0.01	0.01	0.00
			Total Metconazole[d]		0.04	0.16	0.04	0.07	0.08	0.03

Soybean Crop Field Trials	**PMRA 1403171 and 1403181**

GAP: 0.126 kg a.i./ha/season, PHI of 30 days.

Twenty-one field trials were conducted in NAFTA Zones 2, 4 and 5 during the 2004 and 2005 growing seasons. Plots received two broadcast foliar applications of metconazole (formulation, BAS 555 01F, 90 g a.i./L SL) at 0.08-0.09 kg a.i./ha/application, with 9-11-day retreatment intervals, for total seasonal rates of ~0.16-0.18 kg a.i./ha/season (*ca.* 1.4-fold GAP). A nonionic surfactant was used for all applications. Soybean forage and hay were harvested 6-8 days after the last application and soybean seed were harvested 28-32 days after the last application. Soybean hay was allowed to dry in the field for 0-11 days prior to collection. Additional hay samples were collected from two trials 0, 7, 14 and 20-21 days after the last application, and seed samples were harvested 23, 30, 36-37 and 43-44 days after the last application to generate residue decline data. Residues of *cis*- and *trans*-metconazole, M11, M21, M30 and the triazole metabolites (grain only), 1,2,4-T, TA and TAA were quantified using the validated LC/MS/MS method D0508 or method 550/0. Residues of *cis*- and *trans*-metconazole generally declined in soybean forage, hay and seed with increasing preharvest intervals.

Commodity	**Total Application Rate (kg a.i./ha)**	**PHI (days)**	**Analyte**	**Residue Levels (ppm)**						
				n	**Min.**	**Max.**	**HAFT[a]**	**Median[b]**	**Mean[b]**	**Standard Deviation**
Forage	0.16	6-8	*cis*-Metconazole	42	0.40	2.04	1.80	1.14	1.16	0.42
			trans-Metconazole	42	0.07	0.41	0.37	0.22	0.24	0.09
			cis + *trans* (sum)[c]	42	0.47	2.43	2.17	1.37	1.40	0.51
			M11	30	<0.01	0.09	0.09	0.03	0.03	0.02
			M21	30	<0.01	0.03	0.03	0.01	0.02	0.01
			M30	30	<0.01	0.01	0.01	0.01	0.01	0.00
			Total Metconazole[d]	30	0.08	2.46	2.29	1.23	1.30	0.55
Hay	0.16	6-8	*cis*-Metconazole	42	1.00	3.93	3.77	2.08	2.12	0.77
			trans-Metconazole	42	0.17	0.81	0.77	0.40	0.43	0.17
			cis + *trans* (sum)[c]	42	1.17	4.74	4.54	2.48	2.54	0.93
			M11	30	0.02	0.20	0.20	0.06	0.07	0.04
			M21	30	0.01	0.08	0.08	0.04	0.04	0.02
			M30	30	<0.01	0.04	0.04	0.02	0.02	0.01
			Total Metconazole[d]	30	1.21	4.89	4.69	2.70	2.72	1.06
Seed	0.16	28-32	*cis*-Metconazole	42	<0.01	0.04	0.04	0.01	0.01	0.01
			trans-Metconazole	42	<0.01	0.01	0.01	0.01	0.01	0.01
			cis + *trans* (sum)[c]	42	<0.01	0.05	0.05	0.01	0.01	0.01
			M11	30	<0.01	<0.01	0.01	0.01	0.01	—
			M21	30	<0.01	<0.01	0.01	0.01	0.01	—
			M30	30	<0.01	<0.01	0.01	0.01	0.01	—
			Total Metconazole[d]	30	<0.04	0.06	0.06	0.04	0.04	0.01

Sugar Beet Crop Field Trials | **PMRA 1403179**

GAP: 0.225 kg a.i./ha/season, PHI of 30 days.

Twelve field trials were conducted in NAFTA Zones 5, 7, 8, 9, 10 and 11 during the 2005 growing season. At each trial site, one plot received two broadcast applications of metconazole (90 g a.i./L SL) at 0.11 kg a.i./ha/application, with 13-15 day retreatment intervals, resulting in total rates of 0.22-0.23 kg a.i./ha/season (*ca.* 1.0-fold) and a second plot received two broadcast applications at 0.16-0.18 kg a.i./ha/application, with 13-15 day retreatment intervals, resulting in total rates of 0.33-0.35 kg a.i./ha/season (*ca.* 1.6-fold). Mature sugar beet tops (leaves) and root samples were harvested at PHIs of 13-15 days (proposed PHI is 14 days). At two sites, tops and root samples were harvested at PHIs of 1, 7, 14-15, 21 and 27-28 days to examine residue decline. Residues of *cis*- and *trans*-metconazole, M11, M21, M30 and the triazole metabolites (grain only), 1,2,4-T, TA and TAA were quantified using the validated LC/MS/MS method D0508. Residues of *cis*- and *trans*-metconazole generally declined in sugar beet tops and did not increase in sugar beet roots with increasing preharvest intervals.

Commodity	Total Application Rate (kg a.i./ha)	PHI (days)	Analyte	Residue Levels (ppm)						
				n	Min.	Max.	HAFT[a]	Median[b]	Mean[b]	Standard Deviation
Low Rate	Treatment 2									
Tops	0.22-0.23	13-15	*cis*-Metconazole	24	0.01	1.08	1.04	0.03	0.36	0.43
			trans-Metconazole		0.01	0.18	0.17	0.11	0.11	0.05
			cis + *trans* (sum)[c]		0.04	1.26	1.21	0.15	0.47	0.46
			M11		<0.01	0.02	0.01	0.01	0.01	0.00
			M21		<0.01	0.02	0.01	0.01	0.01	0.00
			M30		<0.01	<0.01	<0.01	0.01	0.01	—
			Total Metconazole[d]		0.07	1.29	1.24	0.18	0.50	0.46
Root	0.22-0.23	13-15	*cis*-Metconazole	24	<0.01	0.04	0.04	0.01	0.01	0.01
			trans-Metconazole		<0.01	0.02	0.01	0.01	0.01	0.00
			cis + *trans* (sum)[c]		<0.01	0.05	0.04	0.02	0.02	0.01
			M11		<0.01	<0.01	<0.01	0.01	0.01	—
			M21		<0.01	<0.01	<0.01	0.01	0.01	—
			M30		<0.01	<0.01	<0.01	0.01	0.01	—
			Total Metconazole[d]		<0.04	0.08	0.08	0.05	0.05	0.01
High Rate	Treatment 3									
Tops	0.33-0.35	13-15	*cis*-Metconazole	24	0.01	2.07	1.87	0.05	0.61	0.75
			trans-Metconazole		0.01	0.43	0.38	0.15	0.15	0.11
			cis + *trans* (sum)[c]		0.04	2.49	2.25	0.21	0.76	0.84
			M11		<0.01	0.03	0.03	0.01	0.01	0.01
			M21		<0.01	0.02	0.02	0.02	0.02	0.01
			M30		<0.01	<0.01	<0.01	0.01	0.01	—
			Total Metconazole[d]		0.07	2.53	2.29	0.25	0.80	0.84
Root	0.33-0.35	13-15	*cis*-Metconazole	24	<0.01	0.07	0.07	0.01	0.02	0.02
			trans-Metconazole		<0.01	0.02	0.02	0.01	0.01	0.00
			cis + *trans* (sum)[c]		<0.01	0.09	0.08	0.02	0.03	0.02
			M11		<0.01	<0.01	<0.01	0.01	0.01	—
			M21		<0.01	<0.01	<0.01	0.01	0.01	—
			M30		<0.01	<0.01	<0.01	0.01	0.01	—
			Total Metconazole[d]		<0.04	0.11	0.11	0.05	0.06	0.02

LIMITED FIELD ACCUMULATION IN ROTATIONAL CROPS – LETTUCE, RADISH, SPINACH AND WHEAT	**PMRA 1403183, 1403184 and 1403188**

The submitted limited field accumulation studies were conducted at approximately 0.58 kg a.i./ha (*ca.* 2.6-fold the maximum approved rate). Residues of all analytes except TA and TAA were approximately equal to or below LOQ at all PBIs (31-35, 90, 122-150, 234, 365-396 days). Residues of TA and TAA were widespread and present at levels up to 0.45 ppm and 0.51 ppm, respectively, in wheat grain at PBIs of 396 days.

Metabolites Identified	**Major Metabolites (>LOQ)**	
PBI (days)	**31-35**	**90, 122-150, 234 and 365**
Lettuce	—	—
Spinach	TA, TAA	TA, TAA
Radish Root	TA	TA
Radish Top	*cis*-metconazole, TA, M30	TA
Wheat Grain	TA, TAA	TA, TAA
Wheat Hay	—	—
Wheat Forage	*cis*-metconazole, TA, TAA	TA, TAA
Wheat Straw	*cis*-metconazole	—

PROCESSED FOOD AND FEED	**PMRA 1403171, 1403172, 1403173, 1403174 and 1403175**

The processing studies were conducted at approximately 1.4 to 6.3-fold (soybean), 2-fold (sugar beet) and 13-fold (wheat) the maximum approved rate. Residues of *cis*- and *trans*-metconazole concentrated in wheat AGF (64.3-fold), husks (121.4-fold), course and fine bran (1.9-fold), middlings (2.0-fold) and shorts (2.1-fold); in soybean hulls (1.7-fold); and in sugar beet pulp (1.9-fold), dried pulp (14-fold), thick juice (1.3-fold), molasses (1.9-fold) and raw sugar (2.2-fold).

Crop	**Processed Commodity**	**Average Processing Factor**
Wheat	Aspirated Grain Fractions	64.3
	Cleaned grain	1
	Epidermis/Husk	121.4
	Coarse bran	1.9
	Straight flour	0.2
	Fine bran	1.9
	Middlings	2
	Shorts	2.1
	Germ	1
	Low grade meal	0.7
	Flour type 550	0.3
	Whole meal flour	0.7
	Bread	0.6
Soybean	Hulls	1.7
	Meal	0.6
	Crude oil	0.9
	Refined oil	0.6
	Aspirated Grain Fractions	56

Sugar beet	Pulp (extracted)	1.9
	Pressed (dried) pulp	14
	Pressed water	0.8
	Raw juice	0.9
	Mud (lime sludge)	0.6
	Thin juice	1
	Thick juice	1.3
	Molasses	1.9
	Raw sugar	2.2
	White refined sugar	0.8

LIVESTOCK FEEDING – Dairy cattle **PMRA 1400587**

Nine lactating dairy cows were administered encapsulated metconazole via a balling gun once per day for 29 consecutive days. The average amount of metconazole administered was equivalent to 4.73, 14.58 and 45.65 mg/kg bw/day. Animals were sacrificed within 24-hours of the last dose administration. Samples of milk, fat, muscle, kidney and liver were collected. Samples were analyzed for residues of *cis*-metconazole and *trans*-metconazole in milk, fat, muscle, kidney and liver, as well as, M1 (free + conjugated) and M12 in kidney and liver.

Matrix	Feeding Level (ppm)	Residue Levels (ppm)					
		n	Min.	Max.	Median	Mean	Standard Deviation
cis-metconazole							
Whole Milk	45.65	30	<0.01	<0.01	<0.01	<0.01	—
Skim Milk	45.65	3	<0.01	<0.01	<0.01	<0.01	—
Cream	45.65	3	<0.01	<0.01	<0.01	<0.01	—
Fat	45.65	3	<0.01	<0.01	<0.01	<0.01	—
Kidney	45.65	3	<0.01	<0.01	<0.01	<0.01	—
Liver	14.58	3	<0.01	<0.01	<0.01	<0.01	—
	45.65	3	0.01	0.02	0.01	0.01	0.01
Muscle	45.65	3	<0.01	<0.01	<0.01	<0.01	—
trans-metconazole							
Whole Milk	45.65	30	<0.01	<0.01	<0.01	<0.01	—
Skim Milk	45.65	3	<0.01	<0.01	<0.01	<0.01	—
Cream	45.65	3	<0.01	<0.01	<0.01	<0.01	—
Fat	45.65	3	<0.01	<0.01	<0.01	<0.01	—
Kidney	45.65	3	<0.01	<0.01	<0.01	<0.01	—
Liver	14.58	3	<0.01	<0.01	<0.01	<0.01	—
	45.65	3	<0.01	<0.01	<0.01	<0.01	—
Muscle	45.65	3	<0.01	<0.01	<0.01	<0.01	—
M1 (free + conjugated)							
Kidney	4.73	2	<0.01	<0.01	<0.01	<0.01	—
	14.58	3	<0.01	0.01	<0.01	0.01	—
	45.65	3	0.01	0.03	0.02	0.02	0.01
Liver	4.73	2	<0.01	<0.01	<0.01	<0.01	—
	14.58	3	<0.01	0.01	<0.01	0.01	—
	45.65	3	<0.01	0.05	0.01	0.02	0.02
M12							
Kidney	4.73	2	<0.01	<0.01	<0.01	<0.01	—
	14.58	3	0.01	0.02	0.01	0.01	0.01
	45.65	3	0.01	0.06	0.04	0.04	0.02
Liver	14.58	3	<0.01	<0.01	<0.01	<0.01	—
	45.65	3	<0.01	0.01	0.01	0.01	—

LIVESTOCK FEEDING – Laying hens	**PMRA 1403189**

The applicant submitted a waiver request in lieu of submitting a hen feeding study. The waiver is considered adequate considering that there are no expectations of quantifiable residues in hen matrices. Nevertheless, the submitted hen metabolism data indicated the potential for detectable residues in certain hen matrices so MRLs were proposed at the LOQ of submitted data gathering methods for eggs, fat, meat and meat byproducts. In the situation where rates increase or there is an expansion of use for metconazole, a poultry feeding study may be required.

Livestock Maximum Reasonably Balanced Diet and Anticipated Residues for MRL Setting

Calculation of Livestock Anticipated Dietary Burden in Beef, Dairy, Poultry and Swine

Feedstuff	**Type**	**Max.[1] Residues (ppm)**	**% DM**	**% Diet**				**Maximum Reasonable Dietary Burden (ppm)**			
				Beef	**Dairy**	**Poultry**	**Swine**	**Beef**	**Dairy**	**Poultry**	**Swine**
Wheat hay	R	12.70	88	15				2.16			
Barley grain	CC	1.6	88	50				0.91			
Wheat AGF	CC	6.58	85	5				0.38			
Wheat shorts	CC	0.21	88	25				0.06			
Soybean seed	PC	0.13	92	5				0.00			
Oat hay	R	11.67	90		30				3.89		
Wheat hay	R	12.70	88		15				2.17		
Barley grain	CC	1.60	88		45				0.82		
Soybean seed	PC	0.13	89		10				0.01		
Barley grain	CC	1.60	88			75				1.36	
Soybean seed	PC	0.13	92			25				0.01	
Soybean meal	PC	0.05								0.00	
Barley grain	CC	1.60	88				20				0.36
Wheat shorts	CC	0.21	88				50				0.12
Soybean seed	PC	0.13	89				15				0.01
Totals				**100**	**100**	**100**	**100**	**3.51**	**6.89**	**1.37**	**0.49**

R (roughage); C (carbohydrates); P (protein)

Calculation of the Anticipated Residues for MRL Setting

Matrix	**Maximum Total Residues[2] (ppm)**	**Feeding level (ppm)**	**Transfer Coefficient[3]**	**MRBD (ppm)**	**Anticipated Residues[4] (ppm)**
Cow Milk	0.04	45.65	0.0009	6.89 (dairy)	0.0062
Cow Cream	0.08	45.65	0.0018	6.89 (dairy)	0.0124
Cow Fat	0.04	45.65	0.0009	6.89 (dairy)	0.0062
Cow Kidney	0.04	45.65	0.0009	6.89 (dairy)	0.0062
Cow Liver	0.04	45.65	0.0009	6.89 (dairy)	0.0062
Cow Muscle	0.04	45.65	0.0009	6.89 (dairy)	0.0062
Hen thigh Muscle	0.005	12.6	0.0004	1.37	0.0005
Hen Fat abdo.	0.049	12.6	0.0039	1.37	0.0053
Hen Skin with fat	0.027	12.6	0.0021	1.37	0.0029
Hen Liver	0.034	14.0	0.0024	1.37	0.0033
Hen Egg whites	0.004	12.6	0.0003	1.37	0.0004
Hen Egg yolks	0.010	12.6	0.0008	1.37	0.0011

Swine Fat[5]	0.04	45.65	0.0009	0.49	0.0004
Swine Kidney[5]	0.04	45.65	0.0009	0.49	0.0004
Swine Liver[5]	0.04	45.65	0.0009	0.49	0.0004
Swine Muscle[5]	0.04	45.65	0.0009	0.49	0.0004

[1] Max Residues = *cis*- and *trans*-metconazole.

[2] Maximum Total Residues = *cis*- and *trans*-metconazole. Residue values that were reported to be <LOQ were assigned values of LOQ.

[3] Transfer coefficients were calculated as residue level-to-feed ratios.

[4] Anticipated residues for dietary exposure assessment = Transfer coefficient x MRBD.

[5] Swine transfer coefficients were determined by extending the results of the bovine feeding study to swine.

[a] HAFT = Highest Average Field Trial value.

[b] For residue values reported below the LOQ, the LOQ was used for calculations.

[c] *cis* + *trans* (sum) is the value reported in field trial studies and not the sum of the values presented in these summary tables.

[d] Combined residues of metconazole (sum of *cis* and *trans* isomer) and metabolites M11, M21 and M30, expressed as parent equivalents.

Table 12 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES		
	All primary and rotational Crops, except Barley, Oats, Rye, Wheat	Primary and Rotational Crops of Barley, Oats, Rye, Wheat
RESIDUE DEFINITION FOR MONITORING AND MAXIMUM RESIDUE LIMIT Enforcement method # None	Metconazole†	Metconazole†
RESIDUE DEFINITION FOR RISK ASSESSMENT	Metconazole†	Metconazole† and M11
METABOLIC PROFILE IN DIVERSE CROPS	Similar in all crops examined. M11 was detected in edible portions at high levels in field trial studies.	
ANIMAL STUDIES		
RESIDUE DEFINITION FOR MONITORING AND MAXIMUM RESIDUE LIMIT Enforcement method # None	Metconazole†	
RESIDUE DEFINITION FOR RISK ASSESSMENT	Metconazole† , M12, M1 and M31 and their aglycones	
METABOLIC PROFILE IN ANIMALS	The metabolic profile was similar in goat and hens.	
FAT SOLUBLE RESIDUE	Yes	

DIETARY RISK FROM FOOD AND WATER							
ARfD = 0.002 mg/kg bw/day (♀13-49) ADI = 0.0044 mg/kg bw/day (General Population) ADI = 0.002 mg/kg bw/day (♀13-49) q*=0.0102 (mg/kg/day)$^{-1}$ EEC = 15.9 ug/L	**POPULATION**	**Estimated Acute Risk**		**Estimated Chronic Risk**		**Estimated Lifetime Cancer Risk**	
		%ARfD (95th percentile)		**%ADI**		**Lifetime Risk**	
		Refined Food	Refined Food and Water	Refined Food	Refined Food and Water	Refined Food	Refined Food and Water
	General Population	N/A	N/A	4.2	11.8	1.89×10^{-6}	5.30×10^{-6}
	All Infants (<1 year old)	N/A	N/A	8.9	33.9	N/A	N/A
	Children 1-2 years old	N/A	N/A	15.6	26.9	N/A	N/A
	Children 3-5 years old	N/A	N/A	11.5	22.1	N/A	N/A
	Children 6-12 years old	N/A	N/A	7.1	14.4	N/A	N/A
	Youth 13-19 years old	N/A	N/A	3.7	9.2	N/A	N/A
	Adults 20-49 years old	N/A	N/A	2.8	9.9	N/A	N/A
	Adults 50+ years old	N/A	N/A	2.7	10.2	N/A	N/A
	Females 13-49 years old	19.3	50.1	6.1	21.7	N/A	N/A

† *cis*- and *trans*-metconazole

N/A = not applicable

Table 13 Fate and Behaviour in the Terrestrial Environment

Property	Test substance	Value	Transformation products	Comments
Abiotic transformation				
Hydrolysis	metconazole	Stable at pH 4, pH 5, pH 7, pH9	None	Not a route of transformation
Phototransformation on soil	metconazole	Cyclopentyl label – DT_{50}: 301 days Triazole label – DT_{50}: 304 days	Some minor TPs (less than 2% applied) not identified)	12 hour light,12 hour dark photoperiod, not an important route of transformation
Biotransformation				
Biotransformation in aerobic soil **Bosket sandy loam** soil (pH 6.2, organic carbon 0.3%)	metconazole	Triazole Label – DT_{50}:618 days DT_{90}: 2050 days Cyclo-pentyl Label – DT_{50}: 661 days DT_{90}: 2200 days	- very persistent - Major TP: **M30** - Minor TP: **M11**, **M21** and **M20** (triazole only)	Not an important route of transformation

Property	Test substance	Value	Transformation products	Comments
Biotransformation in anaerobic soil **Sandy loam** soil (pH 6.5, organic carbon 1.6%)	metconazole	Water – DT_{50}: 4.57 days DT_{90}: 36.6 days Soil – n/a Total System – DT_{50}: 800 days DT_{90}: 2600 days	- very persistent - No Major TP - Minor TP: **M30** (detected only once in soil at 1.18%), one unknown at maximum 2.6%	Not an important route of transformation
Mobility				
Adsorption / desorption in soil (Linear, non-Freundlich K_{oc} values)	metconazole	Bosket Sandy Loam – K_{oc}: 2142 mL/g Gardena Clay Loam – K_{oc}: 905 mL/g Penn Silt Loam – K_{oc}: 797 mL/g Lakeland Sand – K_{oc}: 1056 mL/g	Slight Mobility Low Mobility Low Mobility Low Mobility	
Field studies				
Field dissipation – North Dakota	metconazole	DT_{50}: 119 days DT_{90}: 396 days	No TPs detected or identified 12% carryover into the next season (276 days post-application)	Significant detections only in the top 0 - 7.5 cm layer

n/a not available

Table 14 Fate and Behaviour in the Aquatic Environment

Study type	Test material	Value	Transformation products	Comments
Abiotic transformation				
Hydrolysis	metconazole	Stable at pH 4, pH 5, pH 7, pH9	None	Not a route of transformation
Phototransformation in water	metconazole	Purified water: 43 days Pond water: 41 days	**M1**, **M2**, **M3**, **M4**, **M5**, **M7**, **M8** (each less than 7%)	Continuous irradiation for 14 days, not an important route of transformation
Biotransformation				
Biotransformation in aerobic water systems **River Water-Sand** Sediment System (water pH 7.8, total organic carbon 4.5 mg/L; sediment pH 7.2, organic carbon 0.17%)	metconazole	River Water – DT_{50}: 15.9 days DT_{90}: 140 days River Sand – DT_{50}: 206 days DT_{90}: 683 days Total System – DT_{50}: 151 days	Minor TP: **M13**, **M30**, **M21/U1**, **M11/U1**, **M15** Minor TP: **M13**, **M30**, **M21/U1**, **M11/U1**, **M15** Major TP: **M13** Minor TP: **M30**,	

Study type	Test material	Value	Transformation products	Comments
		DT_{90}: 502 days		
Biotransformation in aerobic water systems **Pond Water-Silty Clay Loam** Sediment System (water pH 7.7, total organic carbon 11.0 mg/L; sediment pH 7.3, organic carbon 5.2%)	metconazole	Pond Water – DT_{50}: 0.81 days DT_{90}: 3.95 days Clay Loam – DT_{50}: 534 days DT_{90}: 1140 days Total System – DT_{50}: 900 days DT_{90}: 2990 days	Minor TP: **M30**, **M21/U1**, **M11/U1**, **M15** Minor TP: **M30**, **M21/U1**, **M11/U1**, **M13** Minor TP: **M30**, **M21/U1**, **M11/U1**, **M15**, **M13**	
Biotransformation in anaerobic water systems Water/**Sandy Loam Soil** Sediment System (water pH 7.72 sediment pH 6.5, organic matter 1.6 %)	metconazole	Water Layer – DT_{50}: 4.57 days DT_{90}: 36.6 days Sediment and Total System – DT_{50}: > 120 days DT_{90}: n/a	No Major TP No Minor TP Minor TP: **M30** + one unknown (up to 2.26%)	
Biotransformation in anaerobic water systems *Water/Clay Sediment System* (water pH 7.4 sediment pH 7.0, organic matter 3.5 %)	metconazole	Water Layer – DT_{50}: <1 hour DT_{90}: n/a Sediment and Total System – DT_{50}: > 362 days DT_{90}: n/a	No Major TP No Minor TP No Major TP No Minor TP	
Partitioning				
Bioaccumulation in Fish	metconazole	BCF Values at Low Dose (0.04 mg/L) – Fillet: 63 Viscera: 218 Whole Fish: 128 BCF Values at High Dose (0.40 mg/L) – Fillet: 68 Viscera: 182 Whole Fish: 124		

n/a not available

Table 15 Endpoints Used for Risk Assessment and the Uncertainty Factors Applied

Taxonomic group	Exposure	Endpoint	Species Uncertainty Factor
Earthworm	Acute	LC_{50}	1/2
	Chronic	NOEC	1
Bees	Acute	LD_{50}	1
Other non-target arthropods (Beneficials)	Acute	LR_{50}	1

Taxonomic group	Exposure	Endpoint	Species Uncertainty Factor
Birds	Acute oral	LD_{50}	1/10
	Dietary	LD_{50}	1/10
	Reproduction	NOEL	1
Mammals	Acute oral	LD_{50}	1/10
	Reproduction	NOEL	1
Non-target terrestrial plants	Acute	EC_{25}, or HR_5 of SSD of ER_{50}*	1
Aquatic invertebrates	Acute	LC_{50} or EC_{50}	1/2
	Chronic	NOEC	1
Fish	Acute	LC_{50}	1/10
	Chronic	NOEC	1
Amphibians	Acute	Fish LC_{50}	1/10
	Chronic	Fish NOEC	1
Algae	Chronic	EC_{50}	1/2
Aquatic vascular plants	Chronic	EC_{50}	1/2

Table 16 Toxicity to Non-Target Terrestrial Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]
		Invertebrates		
Earthworm	14-day acute	*cis*-metconazole	**LD_{50}**: > 1000 mg a.i./kg dw **NOEC**$_{(\text{weight loss and mortality})}$: 1000 mg a.i./kg dw	
Bee	96-hour oral	metconazole	**LD_{50}**: 86 µg a.i./bee (highest test concentration) **NOEC**$_{(\text{mortality})}$: 12 µg a.i./bee	Relatively non-toxic
	96-hour contact	metconazole	**LD_{50}**: >100 µg a.i./bee (highest test concentration) **NOEC**$_{(\text{mortality})}$: 100 µg a.i./bee	Relatively non-toxic
		Birds		
Bobwhite quail	14-day acute oral	metconazole 85:15 (*cis:trans*) metconazole 95% (*cis*)	**LD_{50}**: 798 mg a.i./kg bw **NOEL**$_{(\text{weight loss})}$: < 450 mg a.i./kg bw **LD_{50}**: 875 mg a.i./kg bw **NOEL**$_{(\text{weight loss})}$: 450 mg a.i./kg bw	Moderately toxic

Organism	**Exposure**	**Test substance**	**Endpoint value**	**Degree of toxicity[1]**
	8-day acute dietary	metconazole 85:15 (*cis:trans*)	$\mathbf{LC_{50}}$: 1057 mg a.i./kg bw $\mathbf{NOEC}_{(\text{weight loss})}$: < 165 mg a.i./kg diet (lowest test concentration)	Slightly toxic
	Reproduction	metconazole	$\mathbf{NOEC}_{(\text{mortality, sublethal effects})}$: 120 mg a.i./kg diet (highest test concentration) $\mathbf{NOEC}_{(\text{reproduction})}$: 60 mg a.i./kg diet (based on hatching success, chick survival, and chick body weights)	
Mallard duck	Acute	Data not submitted	n/a[2]	
	Dietary	metconazole	$\mathbf{LC_{50}}$: > 5230 mg a.i./kg bw (highest test concentration) $\mathbf{NOEC}_{(\text{weight loss})}$: 1370 mg a.i./kg diet	Practically non-toxic
	Reproduction	metconazole	$\mathbf{NOEC}_{(\text{mortality, sublethal effects, reproduction})}$: 240 mg a.i./kg diet (highest test concentration for all endpoints)	
Mammals				
Rat	Acute	metconazole	NOAEL: 660 mg/kg/bw/day (combined sexes)	Moderate Toxicity
	Acute	Caramba Fungicide	NOAEL: ♂ 3526 mg/kg/bw/day NOAEL: ♀ 2102 mg/kg/bw/day	Low Toxicity
	Reproduction	metconazole	NOAEL: ♂ 9.05 mg/kg/bw/day NOAEL: ♀ 12.67 mg/kg/bw/day	
Mouse	Acute	metconazole	NOAEL: 566 mg/kg/bw/day (combined sexes)	High Toxicity

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]
Vascular plants				
Vascular plant	Seedling emergence	Caramba Fungicide (89 g/L metconazole)	Most sensitive monocot : wheat (plant height) NOEC: 109.8 g a.i./ha EC_{25}: > 109.8 g a.i./ha (highest test concentration) Most sensitive dicot : cabbage (plant height) NOEC: 35.9 g a.i./ha EC_{25}: > 108.7 g a.i./ha (highest test concentration)	
	Vegetative vigour	Caramba Fungicide (89 g/L metconazole)	Most sensitive monocot : none Most sensitive dicot : radish (dry weight) NOEC: 7 g a.i./ha EC_{25}: > 109 g a.i./ha (highest test concentration)	

[1] Atkins et al. (1981) for bees and US EPA classification for others, where applicable

[2] n/a = No study was submitted and no study is required at this time.

Table 17 Toxicity to Non-Target Aquatic Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]
Freshwater species				
Daphnia magna	48-hour acute	metconazole	LC_{50}: 4.2 mg a.i./L NOEC: 3.0 mg a.i./L	Moderately toxic
	21-day chronic	*cis*-metconazole	$LC_{50\ (\text{parent mortality})}$: 1.5 mg a.i./L $EC_{50\ (\text{reproduction})}$: 0.3 mg a.i./L $NOEC_{(\text{ reproduction})}$: 0.16 mg a.i./L	
Rainbow trout	96-hour acute	metconazole	LC_{50}: 2.2 mg a.i./L $NOEC_{(\text{mortality})}$: 0.91 mg a.i./L	Moderately toxic
	28-day chronic	metconazole	LC_{50}: 1.69 mg a.i./L $NOEC_{(\text{mortality and sublethal effects})}$: 0.91 mg a.i./L	
	95-day chronic (early life cycle)	metconazole	LC_{50}: > 0.32 mg a.i./L (highest test concentration) $EC_{50\ (\text{growth})}$: 0.013 mg a.i./L $NOEC_{(\text{sublethal effects})}$: 0.0090 mg a.i./L $NOEC_{(\text{body measurements and mortality})}$: 0.0029 mg a.i./L	

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]
Fathead minnow	96-hour acute	metconazole	LC$_{50}$: 3.9 mg a.i./L NOEC$_{\text{(mortality and sublethal effects)}}$: 1.8 mg a.i./L	
Freshwater green alga	96-hour acute	metconazole	EC$_{50\ \text{(biomass and cell density)}}$: 0.20 mg a.i./L NOEC$_{\text{(biomass)}}$: 0.062 mg a.i./L	
Freshwater diatom	96-hour acute	metconazole	EC$_{50\ \text{(biomass and cell density)}}$: 0.097 mg a.i./L NOEC$_{\text{(biomass, cell density and growth)}}$: 0.031 mg a.i./L	
Aquatic vascular plant	Dissolved 7-day acute	metconazole	EC$_{50\ \text{(frond number)}}$: 0.025 mg a.i./L NOEC$_{\text{(frond number and growth rate)}}$: 0.00051 mg a.i./L	
Marine species				
Crustacean (mysid shrimp)	96-hour acute	metconazole	LC$_{50}$: 0.75 mg a.i./L NOEC$_{\text{(mortality and sublethal effects)}}$: 0.32 mg a.i./L	
	28-day chronic	metconazole	LC$_{50}$: > 180 µg a.i./L (highest test concentration) NOEC$_{\text{(reproduction)}}$: 24 µg a.i./L	
Mollusk (eastern oyster)	96-hour acute	metconazole	EC$_{50}$: 2.3 mg a.i./L NOEC$_{\text{(shell deposition)}}$: 1.0 mg a.i./L	
Marine fish (sheepshead minnow)	96-hour acute	metconazole	LC$_{50}$: 6.3 mg a.i./L NOEC$_{\text{(sublethal effects)}}$: 0.97 mg a.i./L NOEC$_{\text{(mortality)}}$: 4.6 mg a.i./L	Moderately toxic
Marine diatom	96-hour acute	metconazole	EC$_{50\ \text{(cell density)}}$: 1.7 mg a.i./L NOEC$_{\text{(cell density, biomass, growth rate)}}$: 1.1 mg a.i./L NOEC$_{\text{(mortality)}}$: 4.6 mg a.i./L	

[1] US EPA classification, where applicable. If ecotoxicity endpoint values are provided for a particular organism, and the accompanying cell entry for 'degree of toxicity' is left blank, it is because a conventional classification system is not traditionally used for that organism.

Table 18 Screening Level Risk Assessment for Non-Target Invertebrates and Plants

Organism	Test substance: Exposure	Description of Ecotox Endpoint	Ecotox Endpoint Value	Uncertainty Factor	Ecotox Endpoint Value used in Risk Assessment	EEC Value used in Risk Assessment	RQ Value	LOC Exceeded
Invertebrates								
Earthworm	*cis*-metconazole: 14-day acute	**LD$_{50}$:** value is greater than the highest test concentration of 1000 mg a.i./kg dw	1000	2	500	0.0997	0.0002	no

Organism	Test substance: Exposure	Description of Ecotox Endpoint	Ecotox Endpoint Value	Uncertainty Factor	Ecotox Endpoint Value used in Risk Assessment	EEC Value used in Risk Assessment	RQ Value	LOC Exceeded
Bee	metconazole: 96-hour oral	**LC$_{50}$:** 86 µg a.i./bee (converted to 96.32 kg a.i./ha)	86	1	96.32	0.198	0.0021	no
	metconazole: 96-hour oral	**NOEC$_{(mortality)}$:** 12 µg a.i./bee (converted to 13.44 kg a.i./ha)	12	1	13.44	0.198	0.015	no
	metconazole: 96-hour contact	**LD$_{50}$:** value is greater than the highest test concentration of 100 µg a.i./bee (converted to 112 kg a.i./ha)	100	1	112	0.198	0.0018	no
Terrestrial Plants								
Vascular plant	Caramba Fungicide: Seedling emergence	**EC$_{25}$:** values are greater than the highest test concentration for monocots (109.8) and dicots (108.7) g a.i./ha	108.7	1	108.7	233.3 (640-day soil half-life)	2.05	yes
	Caramba Fungicide: Vegetative vigour	**EC$_{25}$:** values are greater than the highest test concentration for both monocots and dicots (109 g a.i./ha)	109	1	109	197.76 (35-day foliar half-life)	1.81	yes
	Caramba Fungicide: Vegetative vigour	**EC$_{25}$:** values are greater than the highest test concentration for both monocots and dicots (109 g a.i./ha)	109	1	109	155.14 (10-day foliar half-life)	1.42	yes

Table 19 Screening Level Risk Assessment for Birds and Mammals

Type of Exposure	Toxicity (mg a.i./kg bw/day)	Feeding Guild (food item)	EDE (mg a.i./kg bw)	RQ
BIRDS				
Small Bird (0.02 kg)				
Acute	79.80	Insectivore (small insects)	7.82	0.10
Reproduction	11.73	Insectivore (small insects)	7.82	0.67

Type of Exposure	Toxicity (mg a.i./kg bw/day)	Feeding Guild (food item)	EDE (mg a.i./kg bw)	RQ
Medium Sized Bird (0.1 kg)				
Acute	79.80	Insectivore (small insects)	6.10	0.08
Reproduction	11.73	Insectivore (small insects)	6.10	0.52
Large Sized Bird (1 kg)				
Acute	79.80	Herbivore (short grass)	6.37	0.08
Reproduction	11.73	Herbivore (short grass)	6.37	0.54
MAMMALS				
Small Mammal (0.015 kg)				
Acute	56.60	Insectivore (small insects)	4.50	0.08
Reproduction	9.05	Insectivore (small insects)	4.50	0.50
Medium Sized Mammal (0.035 kg)				
Acute	56.60	Herbivore (short grass)	14.09	0.25
Reproduction	9.05	Herbivore (short grass)	14.09	0.97
Large Sized Mammal (1 kg)				
Acute	56.60	Herbivore (short grass)	7.53	0.13
Reproduction	9.05	Herbivore (short grass)	7.53	0.83

Table 20 Screening Level Risk Assessment for Non-Target Aquatic Species

Organism	Test Substance: Exposure	Description of Ecotox Endpoint	Ecotox Endpoint Value (mg a.i./L)	Un-certainty Factor	Ecotox Endpoint Value (mg a.i./L) used in R/A	Water Depth (cm)	EEC value used in R/A (mg a.i./L)	RQ	LOC exceeded
Freshwater Species									
Daphnid (*Daphnia magna*)	metconazole: 48- hour acute	**LC_{50}**	4.2	2	2.1	80	0.0218	0.01	no
	metconazole: 21-day chronic	**NOEC** (reproduction)	0.16	1	0.16	80	0.0218	0.14	no

Organism	**Test Substance: Exposure**	**Description of Ecotox Endpoint**	**Ecotox Endpoint Value (mg a.i./L)**	**Uncertainty Factor**	**Ecotox Endpoint Value (mg a.i./L) used in R/A**	**Water Depth (cm)**	**EEC value used in R/A (mg a.i./L)**	**RQ**	**LOC exceeded**
Rainbow Trout (*Salmo gairdneri*)	metconazole: 96-hour acute	**LC$_{50}$**	**2.2**	10	0.22	80	0.0218	0.10	no
	metconazole: 28-day Chronic-Juvenile Growth	**NOEC** (mortality and sublethal effects)	1.14	1	1.14	80	0.0218	0.02	no
	metconazole: 95-day ELS	**NOEC** (sublethal effects)	0.009	1	0.009	80	0.0218	2.42	yes
	metconazole: 95-day ELS	**NOEC** (body measurements and mortality)	**0.0029**	1	0.0029	80	0.0218	7.52	yes
Fathead minnow (*Pimephales promelas*)	metconazole: 96-hour acute	**LC$_{50}$**	3.9	10	0.39	80	0.0218	0.06	no
Green Algae (*Selenastrum capricornutum*)	metconazole: 96-hour acute	**EC$_{50}$** (biomass and cell density)	0.2	2	0.1	80	0.0218	0.22	no
Diatom (*Navicula pelliculosa*)	metconazole: 96-hour acute	**EC$_{50}$** (biomass and cell density)	0.097	2	0.0485	80	0.0218	0.45	no
Aquatic Vascular Plant (*Lemna gibba*)	metconazole: 7-day acute	**EC$_{50}$** (frond number)	0.025	2	0.0125	80	0.0218	1.74	yes
Amphibians	metconazole: Acute - Rainbow	**LC$_{50}$**	**2.2**	10	0.22	15	0.116	0.53	no
	metconazole: Chronic - ELS	**NOEC** (body measurements and mortality)	**0.0029**	1	0.0029	15	0.116	40.00	yes
Marine Species									
Mysid shrimp (*Mysidopsis bahia*)	metconazole: 96-hour acute	**LC$_{50}$**	0.75	2	0.375	80	0.0218	0.06	no
	metconazole: 28-day chronic	**NOEC** (reproduction)	0.024	1	0.024	80	0.0218	0.91	no
Eastern Oyster (*Crassostrea virginica*)	metconazole: 96-hour acute	**EC$_{50}$** (shell deposition)	2.3	2	1.15	80	0.028	0.02	no
Sheepshead Minnow (*Cyprinodon variegatus*)	metconazole: 96-hour acute	**LC$_{50}$**	6.3	10	0.63	80	0.0218	0.03	no

Organism	Test Substance: Exposure	Description of Ecotox Endpoint	Ecotox Endpoint Value (mg a.i./L)	Un-certainty Factor	Ecotox Endpoint Value (mg a.i./L) used in R/A	Water Depth (cm)	EEC value used in R/A (mg a.i./L)	RQ	LOC exceeded
Diatom (*Skeletonema costatum*)	metconazole: 96-hour acute	EC_{50} (cell density)	1.7	2	0.85	80	0.0218	0.03	no

▨ Indicates most sensitive aquatic endpoints (LC_{50}, NOEC) value for Acute and Chronic studies to be used as surrogate data for the Amphibian Risk Assessment

Indicates that Refined Assessment is Required.

Table 21 Refined Risk Assessment for Non-Target Terrestrial Species Exposed to Drift of Metconazole

Terrestrial Plants -Ground Application						
Test substance: Exposure	**Ecotox Endpoint Value (g a.i./ha)**	**Screening Level EEC (g a.i./ha)**	**Screening Level RQ**	**Ground Drift EEC (g a.i./ha)**	**Ground Refined RQ**	**LOC Exceeded**
Caramba fungicide: Seedling emergence	108.7	233.3	2.05	13.998	0.129	no
Caramba Fungicide: Vegetative vigour	109	197.764	1.8143	11.866	0.109	no
Terrestrial Plants - Aerial Application						
Test substance: Exposure	**Ecotox Endpoint Value (g a.i./ha)**	**Screening Level EEC (g a.i./ha)**	**Screening Level RQ**	**Aerial Drift EEC (g a.i./ha)**	**Aerial Refined RQ**	**LOC Exceeded**
Caramba Fungicide: Seedling emergence	108.7	233.3	2.05	53.659	0.494	no
Caramba Fungicide: Vegetative vigour	109	197.764	1.8143	45.486	0.417	no

Table 22 Refined Risk Assessment for Non-Target Aquatic Organisms Exposed to Drift of Metconazole

Ground Application

Organism	Exposure: Ecotox Endpoint Description	Ecotox Endpoint Value (mg a.i./L)	Water Depth (cm)	Screening Level EEC (mg a.i./L)	Screening Level RQ	Ground Drift EEC (mg a.i./L)	Ground Refined RQ	LOC Exceeded
Rainbow Trout (*Salmo gairdneri*)	95-day ELS: NOEC (sublethal effects)	0.009	80	0.0218	2.42	0.002	0.187	no
	95-day ELS: NOEC (body measurements and mortality)	0.0029	80	0.0218	7.52	0.002	0.579	no
Aquatic Vascular Plant (*Lemna gibba*)	7-day acute: 1/2 of the EC_{50} (frond number)	0.0125	80	0.0218	1.74	0.002	0.134	no
Amphibians	95-day ELS: NOEC (body measurements and mortality)	0.0029	15	0.116	40.00	0.007	2.4	yes

Aerial Application

Organism	Exposure: Ecotox Endpoint Description	Ecotox Endpoint Value (mg a.i./L)	Water Depth (cm)	Screening Level EEC (mg a.i./L)	Screening Level RQ	Aerial Drift EEC (mg a.i./L)	Aerial Refined RQ	LOC Exceeded
Rainbow Trout (*Salmo gairdneri*)	95-day ELS: NOEC (sublethal effects)	0.009	80	0.0218	2.42	0.005	0.557	no
	95-day ELS: NOEC (body measurements and mortality)	0.0029	80	0.0218	7.52	0.005	1.729	yes
Aquatic Vascular Plant (*Lemna gibba*)	7-day acute: 1/2 of the EC_{50} (frond number)	0.0125	80	0.0218	1.74	0.005	0.401	no
Amphibians	95-day ELS: NOEC (body measurements and mortality)	0.0029	15	0.116	40.00	0.027	9.2	yes

Table 23 Refined Risk Assessment for Non-target Aquatic Organisms Exposed to Metconazole Runoff

Organism	Exposure: Ecotox Endpoint Description	Ecotox Endpoint Value (mg a.i./L)	Water Depth (cm)	Screening Level EEC (mg a.i./L)	Screening Level RQ	Modelled Ecoscenario EEC (mg a.i./L)	Ecoscenario Refined RQ	LOC Exceeded
Rainbow Trout (*Salmo gairdneri*)	95-day ELS: NOEC (sublethal effects)	0.009	80	0.0218	2.42	0.028	3.11	yes
	95-day ELS: NOEC (body measurements and mortality)	0.0029	80	0.0218	7.52	0.028	9.66	yes
Aquatic Vascular Plant (*Lemna gibba*)	7-day acute: 1/2 of the EC_{50} (frond number)	0.0125	80	0.0218	1.744	0.028	2.24	yes
Amphibians	95-day ELS: NOEC (body measurements and mortality)	0.0029	15	0.116	40.00	0.044	15.17	yes

Table 24 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	Yes. 618 – 661 days (aerobic soil biotransformation study – values for the triazole and cyclo-pentyl labels)
	Water	Half-life ≥ 182 days	No. 0.81 – 15.9 days (aerobic aquatic biotransformation study – values for the river/sand and pond/clay loam systems)
	Sediment	Half-life ≥ 365 days	Yes. 534 days (sediment) 900 days (total system) (aerobic aquatic biotransformation study – values for pond / clay loam system)
	Air	Half-life ≥ 2 days or evidence of long range transport	No. Half-life or volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (< 1.23×10^{-5}) and Henry's Law Constant (2.08×10^{-9} atm-m^{3}-mol^{-1}).

TSMP Track 1 Criteria	**TSMP Track 1 Criterion value**	**Active Ingredient Endpoints**
Bioaccumulation[4]	Log $K_{OW} \geq 5$	No. Log K_{ow} = 3.85
	BCF ≥ 5000	No. BCF = 63 (fillet) and BCF = 218 (viscera)
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?		No. Does not meet all four TSMP Track 1 criteria.

[1] All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e., all other TSMP criteria are met).

[2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

[4] Field data (e.g., BAFs) are preferred over laboratory data (e.g., BCFs) which, in turn, are preferred over chemical properties (e.g., log K_{ow})

Table 25 Spray Buffer Zones Required

The spray buffer zones specified in the Table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands), sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats.

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:			
			Freshwater Habitat of Depths:		Estuarine/Marine Habitats of Depths:	Terrestrial habitat
			Less than 1 m	Greater than 1 m	Less than 1 m	
Field sprayer*	Wheat, barley, oats, rye		1	1	0	0
	Soybeans		1	1	0	1
	Sugar beets		2	1	1	1
Aerial	Wheat, barley, oats, rye	Fixed wing	15	1	0	0
		Rotary wing	15	1	0	0
	Soybean	Fixed wing	20	1	0	10
		Rotary wing	15	1	0	10
	Sugar beets	Fixed wing	50	1	1	15
		Rotary wing	40	1	1	15

* For field sprayer application, spray buffer zones can be reduced with the use of drift reducing spray shields. When using a spray boom fitted with a full shield (shroud, curtain) that extends to the crop canopy, the labelled buffer zone can be reduced by 70%. When using a spray boom where individual nozzles are fitted with cone-shaped shields that are no more than 30 cm above the crop canopy, the labelled buffer zone can be reduced by 30%.

Table 26 Summary of Supported Label Claims for Caramba Fungicide

Proposed			Recommendation (based on value assessment)
Disease claim	**Rate**	**Timing of application(s)**	
Diseases on Wheat			
Control of Septoria leaf spot (*Septoria tritici*, *Stagonospora nodorum*)	0.5 to 0.7 L product/ha	Apply once prior to disease development or at the onset of the disease symptoms.	Supported.
Control of Tan Spot (*Pyrenophora tritici-repentis*)			
Control of Leaf Rust (*Puccinia recondita*)			
Suppression of Fusarium head blight (*Fusarium graminearum)*	1.0 L product/ha	Apply once when crops are at 20% flowering (GS 61-63).	Supported.
Diseases on Barley			
Suppression of Fusarium head blight (*Fusarium graminearum)*	1.0 L product/ha	Apply once between full head emergence to up to 3 days after full emergence of main stem heads.	Supported.
Diseases on Oats and Rye			
Suppression of Fusarium head blight (*Fusarium graminearum)*	1.0 L product/ha	Apply once when crops are at 20% flowering (GS 61-63).	Supported.
Diseases on Soybean			
Control of Asian Soybean Rust (*Phakopsora pachyrhizi*)	0.7 L product/ha	Can be applied from vegetative through full seed (R6 stage) soybeans. For optimal soybean rust control, make initial application between early flowering and pod set (R1 and R3 growth stage), or prior to rust development. If environmental conditions favour continued rust development or if monitoring shows active rust symptoms, repeat application 10-21 days after the first application. Use the shorter interval when rust pressure is high.	Supported.
Diseases on Sugarbeet			
Control of Cercospora leaf spot (*Cercospora beticola*)	1.0 to 1.25 L product/ha	Apply Caramba Fungicide prior to disease development or at the onset of Cercospora leaf spot. Use the higher rate when disease pressure is high. If necessary, reapply on a 14 day schedule to a maximum of two (2) applications.	Supported.

GS growth stage; R1 soybean beginning bloom stage; R3 soybean beginning pod stage; R6 soybean full seed stage

Table 27 Summary of Conditionally Supported Label Claims for Caramba Fungicide

Aerial Application		
Aerial application of Caramba Fungicide on cereals (barley, oats, rye and wheat), soybeans and sugar beets at the proposed rates.	Apply Caramba Fungicide by air at rates listed in the application rate and timing tables (crop specific) when conditions are favourable for the development of disease in a minimum water volume of 50 L/ha.	Supported conditional registration.

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

Table 1 Differences Between MRLs in Canada and in Other Jurisdictions

Commodity	Canada (ppm)	U.S. (ppm)	Codex* (ppm)
Sugar beets roots	0.15	0.07	There are no Codex MRLs established for Metconazole as of May 31, 2009.

* Codex is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

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4.0 Value

1403111 2007, Part 10: Value - Cereals, DACO: 10.1, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.3, 10.3.1, 10.3.2

1403112 2007, Part 10: Value - Soybeans, DACO: 10.1, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.3, 10.3.1, 10.3.2

1403113 2007, Part 10: Value - Sugar beets, DACO: 10.1, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.3, 10.3.1, 10.3.2